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Volume V

May 1973

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NATIONAL HEART, BLOOD VESSEL, LUNG AND BLOOD PROGRAM

VOLUME V
PROGRAM ANALYSIS

PART I

NATIONAL HEART AND LUNG INSTITUTE

MARCH 16, 1973

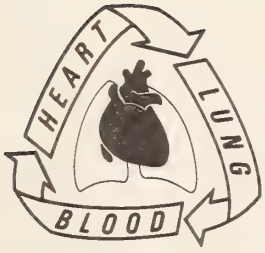
U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service
National Institutes of Health
National Heart and Lung Institute

NATIONAL HEART, BLOOD VESSEL, LUNG AND BLOOD PROGRAM

VOLUME V
PROGRAM ANALYSIS

PART I

NATIONAL HEART AND LUNG INSTITUTE



MARCH 16, 1973

U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service
National Institutes of Health
National Heart and Lung Institute
DHEW Publication No. (NIH) 73–522

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P R E F A C E

Volume V, Program Analysis, is a compilation of program information describing federally supported research efforts relevant to heart, blood vessel, lung and blood diseases and blood resources. The information presented is based on data from fiscal year 1972 (FY 72), the most recent period for which detailed program data are available. An exception is the program (discussed in Part III) of the Environmental Protection Agency for which FY 73 figures are given, since that is the first full year of Agency operation.

Volume V, Program Analysis, is presented in three parts:

Part I - National Heart and Lung Institute

Part II - National Institutes of Health (exclusive of the National Heart and Lung Institute)

Part III - Other Federal Agencies, (USDA, AEC, DOD, EPA, FDA, HSMHA, NASA, NSF, SRS, SSA, DOT, and VA)

Volume V was prepared by the National Heart and Lung Institute with the support and cooperation of the members of the Interagency Technical Committee (IATC) and their respective organizations. The Interagency Technical Committee on Heart, Blood Vessel, Lung and Blood Diseases and Blood Resources, is by law, "responsible for coordinating those aspects of all federal health programs and activities relating to heart, blood vessel, lung and blood diseases and to blood resources to assure the adequacy and technical soundness of such programs and activities and to provide for the full communication and exchange of information necessary to maintain adequate coordination of such programs and activities."

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F O R E W O R D

This report, Part I of Volume V, summarizes National Heart and Lung Institute (NHLI) program activities (exclusive of the NHLI Intramural Program) supported in fiscal year 1972 in 39 categories corresponding to the 39 major problem areas considered by the four advisory panels and supporting task groups in their contribution to the National Heart, Blood Vessel, Lung and Blood Program.

This report is presented in four sections and an appendix.

- Heart and Blood Vessel Diseases--outlines current activities related to eleven major problem areas plus related training programs (Section I).
- Lung Diseases--summarizes current activities related to fifteen major problem areas (Section II).
- Blood Diseases--discusses, in seven problem areas, ongoing research efforts plus describes related training efforts (Section III).
- Blood Resources--outlines current activities being supported in six problem areas with additional data on training programs (Section IV).
- Appendix--Summary of National Heart and Lung Institute Research Grant and Contract Support for fiscal year 1972.

Tables referenced in Sections I through IV of this report are found in the Appendix.

SECTION I

HEART AND BLOOD VESSEL DISEASES

I. HEART AND BLOOD VESSEL DISEASES

Sections 1.1 through 1.11 outline NHLI supported activities correlated with the eleven (11) major problem areas identified by the Heart and Blood Vessel Diseases Panel and its supporting task groups. The eleven areas discussed are:

- Atherosclerosis (1.1)
- Coronary Heart Disease (1.2)
- Peripheral Vascular Disease (1.3)
- Hypertension (1.4)
- Stroke (1.5)
- Congenital Heart Disease (1.6)
- Rheumatic and Other Valvular Heart Diseases (1.7)
- Cardiomyopathy (1.8)
- Arrhythmia (1.9)
- Cardiac Failure (1.10)
- Shock (1.11).

Following this discussion is a statement on training grants and awards in the area of Heart and Blood Vessel Diseases (1.12).

1.1 ATHEROSCLEROSIS

1.1.1 The Framingham Heart Disease Epidemiology Study

This study, a direct operation of the NHLI, has two main objectives: 1) to maintain morbidity and mortality surveillance on the 4,000 survivors of an original cohort of men and women who have participated in a prospective epidemiological study of coronary heart disease, hypertension, stroke, and peripheral vascular disease--as its major concerns, since 1950; and 2) to determine significant factors which are related to the development of these cardiovascular diseases in this general population of participants.

The study, among its many research projects, has addressed itself to:

- A study of the prevalence of abnormal lipoprotein types. This effort, together with the lipoprotein phenotyping of the offspring cohort, will form the basis for a prospective analysis of the relation of lipoprotein types (as currently defined) to the subsequent development of atherosclerotic disease (to be ascertained from continued cardiovascular surveillance) and hence further clarify the atherogenicity of each variety of hyperlipidemia.

- Quantitation of the relative importance of risk factors associated with angina pectoris, myocardial infarction, sudden death, stroke, and congestive heart failure.

- A continuing study of the natural history of arteriosclerosis obliterans (i.e., occlusive disease of the peripheral arteries) which has involved the following of a large representative sample of the general Framingham population and subjecting them to routine periodic medical evaluation documenting all evidence of peripheral occlusive arterial disease obtainable

from a comprehensive longitudinal medical surveillance of the population. The study has examined the manner in which intermittent claudication (peripheral occlusive arterial disease) arises, evolves, becomes complicated by more serious cardiovascular impairments, and terminates fatally.

The findings suggest that it is feasible to identify persons who are vulnerable to occlusive peripheral arterial disease. (The ingredients of this profile are similar to those which predict coronary heart disease.)

1.1.2 The Framingham Offspring Study

The Field Epidemiology Research Section's Offspring Study is a contract supported study designed to evaluate to what extent factors known to increase susceptibility to atherosclerosis and coronary heart disease tend to cluster in families, and to assess the importance of hereditary factors in the development and clinical expressions of atherosclerosis and coronary heart disease. The offspring of the original Framingham Heart Disease Epidemiology Study cohort are being examined (at an age approximating that of the participants in the original cohort at the time of their initial examinations) primarily for aggregation of lipoprotein types, blood pressure, weight pattern, glucose tolerance, and pulmonary flow rates. Approximately 1,200 offspring were examined in fiscal year 1972 and it is anticipated that by mid-1974 (calendar year) upwards of 4,000 of the offspring will have been examined, (FY 72: one contract, totalling $106,804).

1.1.3 Arteriosclerosis Specialized Centers of Research (SCORs)

This is a grant supported program funded and administered by the Atherogenesis Branch, DHVD. The Arteriosclerosis

SCOR program is comprised of a limited number of research centers devoted to the solution of specific, institute defined, high priority problems in arteriosclerosis. The objective of this program is to focus resources, facilities, and manpower on these problems and to expedite the development and application of new knowledge essential for improved diagnosis, treatment, and prevention of arteriosclerotic disease. Generally speaking, the research effort includes multidisciplinary approaches to fundamental and basic aspects, as well as clinical applications and trials.

At present, the Institute funds 15 SCORs in arteriosclerosis (see Table V): FY 72 funding; $9,514,566. While these centers encompass an appreciable amount of the research of the general project grant type, they have also been innovative--moving into three major gap areas in arteriosclerosis research: 1) diagnostic instrumentation, 2) behavior, and 3) pediatrics. In the first area, three centers have teamed with engineering laboratories to develop better invasive and noninvasive instruments to diagnose and characterize atherosclerotic plaques (pulse wave analysis, sonic reflectometry, phono-angiography, hemodynamic modeling, and angiographic image enhancement are under investigation).

Recognizing that arteriosclerotic disease is chronic and subclinical for long periods--and that risk factors for it often involve lifetime habits of smoking, diet, physical activity or asymptomatic hypertension in an individual who generally regards himself as either healthy or only remotely threatened, the arteriosclerosis SCOR program is conducting behavioral research with emphasis on awareness of health, health motivation and compliance with both medical advice and therapy.

Studies in the "pediatric area" are designed to obtain birth to maturity prevalence and longitudinal data about blood cholesterol and blood pressure. Kindred and familial genetics are to be assessed. The association of risk factors in childhood will be related to the occurrence of premature vascular disease in the adult kindred. (In perinatal studies--children born of parents with risk factors are being observed and children of patients in coronary care units with premature myocardial infarctions will be traced and studied.)

1.1.4 Development of Models of Coronary and Aortic Arteriosclerosis in Minipigs for Testing Devices

This contract supported project is funded and administered by the Division of Technological Applications. The primary objective of the project is to develop, standardize, and characterize animal models of advanced coronary and aortic atherosclerosis using Pitman-Moore miniature swine. (FY 72: one contract, totalling $46,802.)

It has been concluded from these studies that both X-rays and high-fat, high-cholesterol diet are needed to produce in these minipigs a severe degree of atherosclerosis in a short time; diet alone will also produce the lesions, but in a longer amount of time. The future direction of this research is to develop a model in which generalized atherosclerosis of significant degree can be produced in swine without the use of X-irradiation. Such a model has already proven useful to test instrumentation designed to detect early developing atherosclerosis.

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1.1.5 Development of Methods to Detect Incipient Failure in Devices

Part of a targeted, contract supported program* of the Division of Technological Applications, NHLI, this project (FY 72: one contract, $79,706) includes an investigation of the acoustic diagnosis of atherosclerosis. Monitoring of developing atherosclerotic lesions is based on the hypothesis that the changes in the arterial wall and those imparted to the flowing blood stream by a plaque will alter the acoustic signature generated in a characteristic fashion.

1.1.6 Lipid Research Clinics

This contract supported, targeted program is funded and administered by the Lipid Metabolism Branch, DHVD. The Lipid Research Clinics Program provides support for a broad collaborative clinical study directly related to improving the detection, diagnosis, and management of hyperlipoproteinemia, determining its prevalence, testing and developing both dietary and drug therapy for specific disorders, and defining the effect of this treatment of premature atherosclerosis.

The objectives of the LRC program include: 1) evaluation of current techniques, and development of better techniques for the diagnosis of hyperlipoproteinemia; 2) improved dietary and drug therapy for specific disorders tested with appropriate controls, randomization, and a double blind design;

* For instrumentation which includes a wide and sophisticated variety of devices and systems for carrying out diagnostic and monitoring functions on the physiologic state of the patient and the physical state of the medical device, for effecting control of a process or device, and for taking corrective or therapeutic action when required.

3) development of prototypes for local programs dealing with hyperlipidemia; 4) facilitation of information exchange about hyperlipoproteinemia through information centers, standard protocols and central data coordination; 5) prevalence surveys to obtain data on the frequency of lipid transport disorders in the population; 6) evaluation of the incidence of atherosclerotic vascular disease in the different types of lipid transport disorders; and 7) a randomized intervention trial to test the efficacy of lipid-lowering therapy in reducing coronary heart disease mortality.

A major collaborative venture of the LRCs is designed to test the hypothesis that lowering of elevated blood lipids in high-risk patients will reduce cardiovascular mortality and morbidity in patients with specific types of hyperlipoproteinemia--and that it will delay the development and/or progression of premature atherosclerosis and cardiovascular disease. This Lipid Clinics Program consists of twelve Lipid Research centers, a coordinating center (i.e., a Central Patient Registry), a central exercise laboratory and a central lipid standardization laboratory.

A nationwide survey to determine the prevalence of lipid transport disorders and their associated CV abnormalities in the population has been initiated. While the studies performed by each clinic will be separate and unique, they will adhere to collaborative protocols which employ standardized means of lipid and CV evaluation as well as means of population sampling, and will involve a total of 150,000-200,000 subjects.

Currently, four prevalence surveys are underway with seven more scheduled to begin in early spring 1973, following certification of their core lab standardization.

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The Lipid Clinics primary prevention trial scheduled to begin active patient recruitment July 1, 1973, will involve an open population of 3,600-4,000 male subjects with Type II hyperlipoproteinemia, ages 35-39 (300 subjects/clinic) who manifest at entry no evidence of vascular disease. The study is based on the use of a specific lipid-lowering drug and diet control, will be based on a fixed protocol, will be double blind, and will last for 5-7 years. (Note: Preliminary plans exist with the USSR for the establishment of two LRCs using standard forms, methods, and prevalence study design.) (FY 72: 12 contracts, totalling $5,475,000).

1.1.7 Multiple Risk Factor Intervention Trial Prevention of Coronary Heart Disease (MRFIT)

This contract supported, targeted program is funded and administered by the Preventive Cardiology Branch, Clinical Applications and Prevention, DHVD. It is a collaborative, fixed-protocol clinical trial designed to test the hypothesis that a preventive program directed at the reduction of serum lipids, reduction of blood pressure, and reduction or elimination of smoking among men, aged 35-54, who are at high risk of coronary heart disease can result in a significant reduction in the incidence of myocardial infarction and death from coronary heart disease (both sequelae of arteriosclerosis).

At present eight clinical centers, a coordinating center, and a central laboratory are funded (FY 72 funding: $3,068,946; see Table VII-B) and involved in the development of the trial protocol, manual of operations, and testing of procedures. To obtain statistically significant results in this trial

it is necessary to utilize a participating population of approximately 12,000 subjects and a regimen to be continued for an observation period of six years for the recording of morbidity and mortality between the intensive management ("treatment") group and the usual care ("control") group.

Based on the experience of other clinical trials, the optimum number of patients to be handled by a team of investigators for this study would require the participation of 600 subjects at each of 20 clinical centers. Presently, proposals submitted in response to RFP-NHLI-73-11 are being reviewed and it is anticipated that 12 additional clinical centers will be selected and funded.

Currently, principal investigators and staff from the present participating centers, serving on the MRFIT Steering Committee and subcommittees are involved in refining and finalizing the trial draft protocol--which it is anticipated will be approved for adoption during this spring of 1973.

1.1.8 Diet Education and Methodology Studies

This contract supported program is funded and administered by the Preventive Cardiology Branch, Clinical Applications and Prevention. The objective of these studies is the development, testing, and evaluation of promising techniques for nutrition education for practical application among individuals with hyperlipidemia to achieve long-term lowering of blood lipids by acceptable changes of eating patterns. Specifically, these studies are designed: 1) to determine how to best counsel and motivate individuals in changing lifetime dietary habits in relation to the prevention and

treatment of cardiovascular diseases, and 2) to conduct an investigation of the application of dietary modifications to reduce hyperlipidemia in the general population. (FY 72: two contracts with total funding of $285,694.)

1.1.9 Nutritional Studies (of the Epidemiology Branch, Clinical Applications and Prevention, DHVD)

These studies are incorporated in contract supported Honolulu-Hiroshima and Puerto Rico studies conducted by the Geographic Diseases Section of the Institute's Epidemiology Branch. The studies are designed to determine, in free living populations, the relationship of dietary habits and dietary nutrient intake to cholesterol, triglycerides and lipoprotein types found in epidemiological surveys, and to determine the relationship of dietary habits and dietary nutrient intake to the prevalence and incidence of CHD as sequelae of atherosclerosis. (Note: Much greater clarification of the role of dietary factors as determinants of lipids within free living populations is needed before undertaking national recommendations relating to modifications of food products or dietary patterns.)

In addition to studying the correlation between serum cholesterol levels and intake of the kind and amount of fat in the diet within free living groups, a methodology has been designed applicable to newly developing clinical trials of the Institute. Practical experience has been accumulated using four principal dietary interview methods; in developing food composition tables for dietary data processing; in formulating coding rules; and in application of epidemiologic principles to dietary data collection. This experience is useful in the Lipid Research Clinics, Multiple Risk Factor Intervention Trial for the Prevention of Coronary Heart Disease, and the Arteriosclerosis SCOR Program.

1.1.10 Behavioral Studies--Research Projects

The Cardiac Functions Branch, Cardiology, DHVD, funds and administers grant supported studies which have as their primary objective the clarification of the role of behavioral and environmental factors in the pathogenesis of cardiovascular and pulmonary disease.

1.1.11 Coronary Drug Project

(See Section 1.2.12 for description of this project.)

1.1.12 Multicategorical Programs

These are grant supported programs which encompass several categorical areas of interest to the Institute. They are usually program projects that involve a number of cooperative investigators, frequently of differing disciplines. Due to the multicategorical nature, the efforts of several disciplines can thus be brought to bear upon problems not falling neatly into a strictly "categorical" interest of the Institute. Hence, such grant programs provide research institutions with a mechanism for fostering broad-based approaches to problems of cardiovascular and pulmonary disease.

These grants also frequently involve both fundamental and clinical research and, thus, foster rapid scientific exchange between basic and clinical scientists.

1.1.13 Research (Grant Supported) in Arteriosclerosis

The Division of Heart and Vascular Diseases funds and administers a program of grant supported research in arteriosclerosis. In FY 72, this program encompassed 145 grants (totalling

$6,983,737)*, which ranged from the most basic studies in molecular structure and function to the evaluation of surgical procedures and the epidemiological description of disease. (For example, investigations in the area are: 1) animal models of arteriosclerosis and coronary heart disease; 2) surgical techniques for revascularization of the heart; and 3) the frequency, extent and severity of arterial lesions which may determine the feasibility of operative treatment.) The program includes studies supported by research project grants and program project grants.

1.1.14 A Twin Study of Genetic Factors in Cardiovascular Diseases

This contract supported study is funded and administered by the Epidemiology Branch, Clinical Applications and Prevention, DHVD, (FY 72: one contract, totalling $85,098).

This study acknowledges that twin studies are potentially the most powerful available for studying genetic factors in human disease, and is designed both: 1) to evaluate the relative contribution of environmental and genetic factors to the development of cardiovascular diseases and 2) to evaluate the relative contribution of environmental and genetic factors to the levels of risk factors associated with cardiovascular disease. Four populations of twins are being studied. Preliminary results to date indicate major genetic determinants of the observed variability in height, weight, and serum cholesterol levels, moderate genetic effects on blood pressure, and virtually no genetic component for the variability in serum triglycerides.

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* Above dollar totals and number of grants do not include the Specialized Centers of Research in Arteriosclerosis: 15 grants, totalling $9,514,566. (See Section 1.1.3 for description of this SCOR program.)

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1.1.15 Analysis of Framingham Heart Study Data

The Field Epidemiology Research Section, Epidemiology Branch, in cooperation with the Biometrics Research Branch and the Framingham Heart Study, has been and is analyzing certain portions of the data generated from this study.

This effort includes a study of the correlation of risk factors among siblings and spouses. The sibling analyses indicate significant familial association of serum cholesterol, relative weight, blood pressure, and smoking habits. These correlations tend to remain stable during middle age when most of the siblings are living apart and thus experiencing somewhat different environmental conditions. This is consistent with the hypothesis that variations in risk factor levels are largely due to genetic effects or environmental differences operating at younger ages.

1.1.16 Honolulu-Hiroshima Study of Coronary Heart Disease and Cerebrovascular Disease

This contract supported study is administered by the Epidemiology Branch, Clinical Applications and Prevention (FY 72: two contracts, one interagency agreement, totalling $134,065). Begun in 1965, this study is designed to test and assess the degree of reported differences in coronary heart disease and cerebrovascular disease in a cohort of 8,000 Japanese men (45-64 years of age) in Hiroshima and Japanese-American men (45-64 years of age) in Hawaii, specifically to delineate the environmental factors responsible for the differences in coronary disease morbidity and mortality of these men of similar ethnic origin but of different geographical location. A confirmed incidence of myocardial infarction and death from coronary heart disease less than half of that found for men

of the same age in Framingham has been found. This lower incidence is present even at similar levels of the three common risk factors of serum cholesterol, blood pressure, and amount of cigarettes smoked. Other factors must be responsible for this lower incidence among Japanese.

1.1.17 Epidemiological Study of Coronary Atherosclerosis in Puerto Rico

This contract supported study is funded and administered by the Epidemiology Branch, Clinical Applications and Prevention (FY 72: one contract, totalling $324,635). Begun in 1965, this project is a study in a U.S. population exhibiting low coronary disease rates and provides a potential for establishing the characteristics which are natural determinants of low coronary disease rates. The study, on 8,301 men ages 45-64, is designed to determine the factors significantly associated with low incidence of myocardial infarction and a low mortality from coronary heart disease in a "natural" U.S. population. From the preliminary trend of findings, it appears that this study will enable us to extend the relationship of heart disease to lipid levels to the lower ranges of cholesterol and triglyceride which have been measured in this population.

1.1.18 The Israel-United States Cooperative Ischemic Heart Disease Study

This P.L. 480 study*, administered by Clinical Applications and Prevention, is a prospective epidemiological study of

* This refers to collaborative health research and research-related projects abroad which are supported entirely by foreign currencies owned by the U.S. which have been determined by the U.S. Treasury to be in excess of normal U.S. needs in the countries. The program helps achieve the domestic health objectives of DHEW and promotes U.S. foreign policy.

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hypertension and ischemic heart disease. It is designed to determine, in a population of 10,232 male Israeli civil servants age 40 and over, the biologic characteristics (including physical measurements, biochemical, dietary and psychosocial measurements) of an adequate population representing diverse ethnic and geographic origins and differing in prevalence of cardiovascular diseases, so as to allow the ascertainment of evidence of morbidity and mortality from ischemic heart disease and hypertension in relation to the measured characteristics. The study is also designed to: 1) determine whether factors established as related to coronary heart disease risk elsewhere are also important in this heterogeneous population, and 2) evaluate whether early environmental factors as reflected by country of origin of the migrant population in the study are related to important differences in the incidence of coronary heart disease. To date, all basic data have been edited and placed on computer tape. A series of tabulations are systematically being produced to look at univariate and multivariate risk factor relationships to incidence of ischemic heart disease, hypertension, diabetes, peripheral vascular disease and also analysis of data on pulmonary function measurements.

1.1.19 Epidemiological Investigation of Ischemic Heart Disease and Hypertension in Yugoslavia

This P.L. 480 study, administered by Clinical Applications and Prevention, involves a population cohort of 11,121 men aged 35-64 from two Yugoslavian communities who are being followed through examination procedures made comparable to those in the Framingham Heart Disease Study. The principal

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cardiovascular diseases studied are coronary (ischemic) heart disease and hypertension. The pertinent objectives of this study are: 1) to determine the incidence of coronary heart disease in two populations; one rural, the other mainly industrialized; and 2) to determine the relationship between incidence rates and ethnic origin, nature of diet, occupation, physical activity, body type, and personal habits (such as use of alcohol) in these populations suspected to have very low rates of coronary heart disease. To date, the annual incidence of myocardial infarction and coronary heart disease death was established to be 1.8 per 1,000 in comparison with the Framingham rate (9.4 per 1,000) which is an incidence of 19 percent of the comparable Framingham rate. Risk factor associations have not yet been determined from the small number of incidence cases. This will be done when the data from the present examination cycle are completed within the next year. Having identified the very low rate of myocardial infarction incidence experienced by these populations, there is now the opportunity to search for possible protective factors in this population.

1.2 CORONARY HEART DISEASE

1.2.1 Framingham Heart Disease Epidemiology Study

This study, a direct operation of the NHLI, which deals with clinical end points and focuses on etiological mechanisms has two main objectives: 1) to maintain morbidity and mortality surveillance on the 4,000 survivors of an original cohort of men and women who have participated, since 1950, in a prospective epidemiological study of coronary heart disease, hypertension, stroke, and peripheral vascular disease; and 2) to determine significant factors which are related to the development of these cardiovascular diseases in this general population of participants.

This study has continued active production of reports of findings from the study population which has been examined and studied over a 16-year period.* Detailed individual publications have been produced on findings relating to coronary heart disease, sudden death, and on unrecognized or silent myocardial infarction.

Significant in the accomplishments of this study is the demonstration that elevated systolic and diastolic blood pressure, serum cholesterol, glucose intolerance, cigarette smoking, and LVH on ECG are of importance for coronary heart disease and

* In terms of examination cycles, at present complete data is available only over the first 16 years.

for the elucidation of the relative importance of factors of risk in the pathogenesis of coronary heart disease. Additionally, the study has among its activities:

- Developed a coronary profile handbook.
- Addressed itself to study the evolution of cardiovascular disease.
- Concerned itself with elucidating the natural history of myocardial infarction.
- Elucidated factors relating to sudden death (including: ECG precursors of sudden death--and the role of obesity in sudden death).
- Concerned itself with elucidating factors related to the development of coronary heart disease in women.
- Begun an analysis of the rate of infarction and sudden death--also of the rate of congestive heart failure, strokes, and survival--in subjects who developed angina pectoris or myocardial infarction under observation (which could provide information to evaluate efficacy of surgical intervention for ischemic heart disease).
- Concerned itself with elucidation of familial and spouse aggregation of coronary heart disease and associated risk factors.

Additional related studies include:

- A study of the Disability of Stroke Victims (cross reference: Section 1.5.1) has been implemented, thus further describing the epidemiology of stroke in the Framingham Study Population. The functional, social, and vocational status of persons who have survived completed stroke are assessed at least 6 months after occurrence of the stroke. These assessments permit a correlation of functional, social and vocational outcomes as well as survival with the various types of stroke. With appropriate analyses, it will be possible to look at the relationship between precise location of the lesion in

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completed stroke, the comorbid processes, and relate these to social, vocational, other host characteristics and functional factors as well as to survival.

- An Epidemiological Study of Brain Infarction Associated with Occlusive Arterial Disease (cross reference: Section 1.5.1). Evidence from this, and other studies, has resulted in the emergence of certain patterns which suggest certain risk factors for stroke. Hypertension has been shown to clearly be the most important contributor to stroke incidence. Diabetes and hyperlipidemia have also been shown to be of importance. Certain combinations of risk factors have been shown to carry more risk than do the same items singly; a compounding of risk that has pathogenetic, preventive, and public health implications.

(This study has also shown that for purposes of stroke screening alone the most efficient and practical method is to determine casual blood pressure. Also shown is the fact that various types of arterial occlusion with cerebral infarction are by far the most prevalent causes of stroke.)

- One of the projects supported by this study deals with factors related to suddenness of coronary deaths; another with ECG precursors of sudden death; a third with the evolution of intraventricular conduction disturbances (cross reference: Section 1.9.1).

  Specifically, the first phase of a Framingham-Albany collaborative study on sudden death has been completed. Precursors of sudden death have been analyzed and presented. The next phase of the study--concerned with factors related to the suddenness of coronary fatality (i.e., particularly related to sudden death)--is underway. The final phase will involve a detailed examination of the ECG precursors of sudden death.

1.2.2 Framingham Offspring Study

This project* is described in the section on atherosclerosis. Its design and objective are as applicable to coronary heart disease as to atherosclerosis.

1.2.3 A Twin Study of Genetic Factors in Cardiovascular Disease*

(See Section 1.1.14 for topic description.)

1.2.4 Analysis of Framingham Heart Study Data*

(See Section 1.1.15 for topic discussion.)

1.2.5 Honolulu-Hiroshima Study of Coronary Heart Disease and Cerebrovascular Disease*

(See Section 1.1.16 for topic description.)

1.2.6 Epidemiological Study of Coronary Atherosclerosis in Puerto Rico*

(See Section 1.1.17 for topic description.)

1.2.7 Nutritional Studies (of the Epidemiology Branch, Clinical Applications and Prevention, DHVD)

(See Section 1.1.9 for topic description.)

* which deals with clinical end points, and has a focus upon etiological mechanisms.

1.2.8 The Israel-United States Cooperative Ischemic Heart Disease Study*

(See Section 1.1.18 for topic description.)

1.2.9 Epidemiological Investigation of Ischemic Heart Disease and Hypertension in Yugoslavia*

(See Section 1.1.19 for topic discussion.)

1.2.10 Multiple Risk Factor Intervention Trial for the Prevention of Coronary Heart Disease (MRFIT)

(See Section 1.1.7 for topic description.)

1.2.11 Lipid Research Clinics (LRCs)

(See Section 1.1.6 for topic description.)

1.2.12 Coronary Drug Project (CDP)

This is a grant supported clinical trial funded and administered by the Clinical Trials Branch, Clinical Applications and Prevention. The trial is designed to determine whether the mortality rates of men who have coronary heart disease and who have had one or more documented heart attacks can be significantly improved by the use of lipid-lowering drugs. This study is also designed to determine: 1) the ability of four lipid-lowering drugs (clofibrate, nicotinic acid, conjugated equine estrogens, and a placebo) to reduce mortality and recurrences from myocardial infarction among men who have already experienced one or more proven myocardial infarctions;

* which deals with clinical end points, and has a focus upon etiological mechanisms.

and 2) to determine whether the degree to which these drugs change serum lipids is correlated with any effect on mortality and morbidity rates.

This randomized clinical trial involves 53 participating grantee clinics, a coordinating center, a control laboratory, and drug distribution center--and is administered by the NHLI, the CDP Policy Advisory Board, and the CDP Steering Committee. The project is a fixed protocol cooperative study involving random and double-blind assignment of patients to one of six drug regimens. The 8,400 patients are men 30-64 years of age. After allocation to treatment, patients are followed at the clinics for 5 years or until death.

Analysis of clinical data and mortality rates from myocardial infarction in the placebo-control group has revealed a number of clinical and electrocardiographic characteristics which are highly predictive of risk of myocardial infarction recurrence and death from coronary heart disease. This should be of value in any efforts to either develop or apply management regimens for patients who have survived their initial attack of myocardial infarction.

Nearly three-fourths of the participants have completed 5 years of follow-up on their allocated drug regimens. Thus far there has been a clear indication that the estrogen (5.0 mgm/day) and dextrothyroxine (6.0 mgm/day) treatments have unacceptably high adverse effects and should not be used for secondary prevention in coronary patients. Results with the remaining drug regimens are expected to be completed by the termination of this study in early 1975.

1.2.13 Coronary Drug Project--Aspirin Study

This is a grant supported clinical trial funded and administered by the Clinical Trials Branch, Clinical Applications and Prevention. Using a study population of 1,250 Coronary Drug Project patients, this is a randomized, prospective, secondary prophylactic trial in males who have survived one or more myocardial infarctions. The scientific basis for the study includes the well documented inhibiting effect of acetylsalicylic acid on platelet aggregation (the first stage of arterial thrombogenesis); the clinical significance of this phenomenon is unknown, but data from an unpublished retrospective hospital surveillance study suggest possible benefits of regular aspirin treatment in reducing the incidence of acute myocardial infarction.

1.2.14 Diet Education and Methodology Studies

(See Section 1.1.8 for topic description.)

1.2.15 Cardiac Transplantation*

The Institute supports a small but broad based, grant funded program in cardiac transplantation comprised of a number of basic and animal studies. Particularly promising are some of the investigations dealing with problems of rejection.

* While this program may more appropriately belong in the section on heart failure, mention of transplantation in the Panel Report on Heart and Blood Vessel Diseases appears in both the section on heart failure and the section on coronary heart disease; hence its appearance here.

NHLI also supports, by grant, one large program in clinical cardiac transplantation. A small number of highly selected, very carefully studied patients are receiving transplants. This group's survival record has been excellent. Further, important immunological and physiological data are resulting from the study of these patients. This program is, at the same time, pursuing a program in animal transplantation (FY 72: $1,212,000).

1.2.16 Sudden Cardiac Death

The Institute's Clinical Cardiology Branch funds and administers a contract supported program in the area of sudden cardiac death. (In FY 72, 15 contracts, totalling $1,701,920 were supported.)

The objectives of this program are:

- To Develop methods for identifying subgroups in the population chronically at high risk for sudden death.
- To develop the means of better recognition of premonitory warning signs.
- To identify and characterize possible precipitating factors and pathophysiological processes.
- To develop and assess means of early therapy of the suspected heart attack victim--to prevent sudden death.

These objectives are being met by a number of activities which include:

- Epidemiological studies to define risk factors.

- Collaborative clinical-pathological correlation of sudden cardiac death (using medical examiners resources and interviews).

- Exploration of early therapy and emergency medical services using:

  - Specially equipped ambulance systems.

  - Paramedical personnel--trained to make significant observations and judgements, administer emergency electrical defibrillation, and administer intramuscular and intravenous medications, and conventional cardiopulmonary resuscitative procedures.

- A study to evaluate the effects of anti-arrhythmic agents which can be self-administered by a rapidly acting route.

- A study designed to characterize electrophysiological and mechanical characteristics of the dog heart during the phase of recovery from myocardial ischemia--as a model for the pathogenesis of arrhythmias which could, in humans, lead to sudden cardiac death.

1.2.17 Medical Facility Utilization During Acute Coronary Episodes

This contract supported project is funded and administered by the Epidemiology Branch, Clinical Applications and Prevention. The objective of this project is to describe the course taken by persons experiencing acute coronary episodes and to distinguish physiological, social, cultural, or geographic factors that may have influenced the course of events. Recognizing that the utilization of health care facilities in the hours immediately following an acute coronary event probably enhances the patient's chances of survival, this study attempts to elucidate those factors which influence the patient's decision to seek or not to seek medical attention

in the hours following the onset of coronary symptoms. Particular attention has been given to the differences between in-hospital patients and those who died without reaching the hospital with a view to possible intervention.

1.2.18 Physiological and Biochemical Processes Fundamental to New Therapeutic Methods--Protecting the Ischemic Myocardium

The Clinical Cardiac Diseases Branch, DHVD, funds and administers a contract supported program, (FY 72: 12 contracts, totalling $916,779) the objective of which is to develop interventions to protect ischemic myocardium, to minimize infarct size and/or to enhance myocardial repair, including experimental studies of the physiology and biochemistry of ischemic myocardium and myocardial scar information fundamental to the development of such interventions.

During FY 72, the first year of contract operation, each contractor acquired the necessary facilities, equipment, and personnel required for his or her project. Each developed or obtained the animal model preparation most suitable for individual needs, and each has resolved technical difficulties so as to give reliable results. Considerable cooperation and interchange of ideas and techniques between the contractors on animal model preparations has grown to include collaborative efforts between individual contracts on the research itself.

Progress toward the scientific objectives of the contracts has been made in a relatively short period of time. For example: 1) it has been found that in contrast to hypoxia

which increases glucose utilization in association with depletion of high-energy phosphates, ischemia produces the same depletion without a compensatory increase in glucose utilization; and 2) intriguing biochemical and electron microscopic findings suggest that lysosomal activity may be inappropriately elevated and contribute to the destructive effects of ischemia. Many of the findings resulting from this contract supported research and concerning the underlying mechanisms of myocardial cell injury and death due to ischemia have important implications and hold theoretical promise for the eventual development of interventions to counter the destructive effects of ischemia.

Further, these studies include efforts which have resulted in the synthesis of polypeptide analogs of angiotensin. These have been shown to stimulate mitochondrial ATP production and possess significant inotropic effects under hypoxic conditions with very little vasoconstrictor effects. In addition to the obvious therapeutic implications regarding increasing oxygen efficiency in the ischemic heart, these studies hold promise of significant new basic understanding of hormone effects on subcellular processes such as mitochondria and protein kinase.

1.2.19 Acute Myocardial Infarction--Quantifying Infarct Size

The Clinical Cardiac Disease Branch, DHVD, funds and administers a contract supported program, (FY 72: three contracts, totalling $155,004), the objective of which is to develop a method to determine the amount of myocardium affected by infarction and/or ischemia. Of great importance for therapy, this method would be applicable safely to large numbers of

patients, provide information on the natural progressions of the disease, yield results rapidly and reproducibly, and be repeatable to monitor the impact of experimental and therapeutic interventions on the extent of myocardial damage.

At present, two research projects are exploring a variety of radionucleides and radiopharmaceuticals for "imaging" acute myocardial infarction in patients. A third project is exploring and assessing the feasibility of new ultrasonic techniques for accurately detecting and sizing damaged myocardium.

In addition to this effort several Myocardial Infarction Research Units (MIRUs) are exploring ways of sizing infarcts: epicardial unipolar and pericardial electrodes are used to map out the extent of ST segment elevation in ischemia and/or infarction; serial serum and myocardial creatine phosphokinase activities are assessed to estimate the degree and extent of myocardium affected. These techniques have been implemented in MIRU-conducted clinical studies.

1.2.20 Myocardial Infarction Research Units (MIRU)

The Clinical Cardiac Diseases Branch, DHVD, funds and coordinates the contract supported MIRU program (FY 72: nine contracts, totalling $4,865,668).

The general goal of this program is the better understanding of acute myocardial infarction, with particular emphasis on underlying causes, clinical manifestations, and optimum management. The major focus of research has been in the clinical area encompassing a wide range of subjects including chemical characterization, prognostic factors (natural course

of the disease), therapeutic interventions, and new methodology. These studies involve cardiac physiology, enzymology, electrophysiology, respiratory physiology, biochemistry, hematology, surgery, pathology, pharmacology, radiology, psychology, nuclear medicine, and computer sciences.

Specific program objectives include:

- The development of rapid, precise, and sensitive diagnostic methods for the identification of myocardial infarction and/or its extension.
- Characterization of the pathophysiological processes and underlying pathology involved in acute myocardial infarction and the interaction of the various organ systems.
- Identification of the pathophysiology and developments of prophylaxis and therapy of rhythm and conduction derangements (see section on arrhythmias) in acute myocardial infarction.
- Identification of the pathophysiology and development of prophylactic and therapeutic techniques for heart failure (see section on congestive heart failure) and shock (see section on shock) by pharmacological, mechanical assist, surgical, and other techniques.
- Identification of the pathophysiology and development of prophylactic therapeutic techniques for other complications of acute myocardial infarction.
- Development of indicators of short- and long-term prognosis.
- Development of measurement methods, instrumentation, and on-line data acquisition, processing, storage, and analysis capabilities for clinical investigation of acute myocardial infarction, including techniques which ultimately will be of widespread clinical use.

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- The conduct of laboratory studies fundamental to the clinical investigation.
- Education and dissemination of information.

1.2.21 A Study of Seasonal Mortality in 1967 for Chicago, Illinois

In FY 72 this study was funded and administered by the Biometrics Research Branch, Clinical Applications and Prevention (funded from the Branch direct operating funds). Its objective is to study the relation of a number of climatological factors to mortality from cardiovascular disease, respiratory disease, and other diseases. In particular, to examine the association between coronary deaths and snowfall--and also, to evaluate data on sudden deaths from coronary heart disease for seasonal patterns.

1.2.22 A Study of Cardiovascular Mortality and Weather in New York City for 1967

In FY 72 this study was funded and administered by the Biometrics Research Branch. The objective of this investigation (funded by direct operating funds) is to study the relation between a number of climatological factors to mortality from cardiovascular disease, respiratory disease, and other diseases--with emphasis on an examination of the association between coronary deaths and snowfall.

1.2.23 Artificial Devices and Total Heart Replacement

(See descriptions of this topic in section on cardiac failure.)

1.2.24 Cardiac Arrhythmias

(A program supported by both grants and contracts, funded and administered by the Cardiac Functions Branch and the Clinical Cardiac Diseases Branch, is described in the section on arrhythmias.)

1.2.25 Cardiovascular Dynamics

(See Section 1.10.3 for topic description.)

1.2.26 Studies Dealing with the Prevention of Coronary Atherosclerosis and Hypertension

(See sections on atherosclerosis and hypertension for appropriate topic descriptions.)

1.2.27 Multicategorical Programs

(See section 1.1.12 for topic description.)

1.2.28 Bioinstrumentation--Oxygenators

The Instrumentation Branch, Division of Technological Applications, supports the development and improvement of new or existing blood oxygenation techniques for short-term use in presently existing extracorporeal perfusion systems for open heart surgery*. The concepts which have been supported are those which eliminate the blood-air interface (which has been shown to damage blood by denaturation of blood proteins and destruction of cellular elements) and to replace it with a liquid/liquid or a blood/membrane interface.

* The major applicability of extracorporeal oxygenators is in the areas of Congenital and Rheumatic Heart Disease.

As the program has progressed, concepts have been supported in which oxygenators have been fabricated from materials that are more thrombo-resistant, and attempts have been made to improve the hemodynamic design of blood oxygenators in an effort to reduce thrombus formation further by eliminating areas of stagnation and turbulent blood flow. During FY 72, efforts have been directed toward developing materials that both meet the specifications with regard to gas transfer and thrombo-resistance and are inexpensive to produce. Emphasis has also been on oxygenator development in: 1) liquid/liquid interface oxygenators; 2) capillary membrane oxygenators; 3) combination pump oxygenators; and 4) the development of ultrathin membranes.

A listing of projects is as follows:

- Feasibility of study of the use of polysulfone in oxygenation.
- Testing and evaluation of blood oxygenators.
- Development and evaluation of a new and improved oxygenator.
- Fabrication of oxygenators using specified materials.
- The development of a capillary oxygenator.
- Examination and evaluation of fluorocarbons for use in liquid membrane oxygenators.
- Fabrication of oxygenators using specified material.
- Development of a pump oxygenator.
- Provide ultrathin membranes for evaluation in blood oxygenators.

1.2.29 Biomaterials

(See Section 1.10.6 for topic description.)

1.2.30 Fundamental Research

Studies in this program area are those involving research which is basic to many areas of the Heart and Lung Institute mission but which have a single discipline approach. (See Section 1.10.4 for topic description.)

1.2.31 Research Projects (Grant Supported) in Coronary Heart Diseases

Currently the Clinical Cardiac Diseases Branch and Cardiac Functions Branch, Cardiology, and predominantly the Atherogenesis Branch, Etiology of Arteriosclerosis/Hypertension fund and administer a grant supported program in coronary heart disease which is encompassed under headings ranging from "Coronary Heart Disease," "Arteriosclerosis," "Cardiodynamics," "Heart Failure and Shock," and "Arrhythmias" to "Multicategorical Programs" and "Fundamental Research" (see appropriate topic descriptions).

1.2.32 Emergency Medical Services

The Clinical Cardiac Diseases Branch funds and administers programs of emergency medical services. The use of specially equipped ambulance systems in three centers has not only provided information on the early pathophysiology of

myocardial infarction and sudden death, but has demonstrated the feasibility of training paramedical personnel to make significant observations and judgements in cases of cardiovascular emergencies, to obtain EKG signals for transmission, to administer emergency electrical defibrillation, and to administer intramuscular and intravenous medications in addition to the conventional cardiopulmonary resuscitative maneuvers. These studies have demonstrated the advantage and need for a comprehensive emergency system which is capable of managing cardiovascular problems, rather than for unique cardiovascular teams.

1.2.33 Arteriosclerosis Specialized Centers of Research

(See Section 1.1.3 for topic description.)

1.3 PERIPHERAL VASCULAR DISEASE

1.3.1 Research (Grant Supported) in Peripheral Vascular Disease

The Clinical Cardiac Disease Branch, Cardiology, funds and administers a program of grant supported studies in peripheral vascular disease (FY 72: 31 grants, totalling $1,503,266), which ranges from studies of clinically manifested peripheral arterial and venous vascular disease, to diagnosis, to studies of medical and surgical therapies.

1.3.2 Research (Grant Supported) in Arteriosclerosis

(See Section 1.1.13 for topic description.)

1.3.3 Arteriosclerosis Specialized Centers of Research

(See Section 1.1.3 for topic description.)

1.3.4 Diet Education and Methodology Studies

(See Section 1.1.8 for topic description.)

1.3.5 Nutritional Studies

(See Section 1.1.9 for topic description.)

1.3.6 The Framingham Offspring Study

(See Section 1.1.2 for topic description.)

1.3.7 Israel-U.S. Cooperative Ischemic Heart Disease Study

((See Section 1.1.18 for topic description.)

The incidence of peripheral vascular disease is being recorded. This is one of the items subjected to univariate and multivariate analysis.

1.3.8 Honolulu-Hiroshima Study of Coronary Heart Disease and Cerebrovascular Disease

(See Section 1.1.16 for topic description.)

1.3.9 Epidemiological Study of Coronary Atherosclerosis in Puerto Rico

(See Section 1.1.17 for topic description.)

1.3.10 Biomaterials

The Biomaterials Branch, Division of Technological Applications has as one program goal the development of a practical capability to generate a biologically satisfactory blood/artificial device or prosthetic surface interface. The activities designed to attain this goal are of import to the continuing refinement of prosthetics (which must be constructed of material that neither affect nor are affected by blood and/or tissue and that retain intrinsic qualities of elasticity and strength for years of constant use in such an environment).

Selected projects funded (by contract) by this branch, and pertinent to peripheral vascular disease, are:

- Development of intimal linings.
- Development of micro-flocked surfaces.
- Development and evaluation of a new biomaterial forr membrane lungs.
- Thermodynamic studies of interactions of blood with foreign surfaces.
- Further characterization of the TDMAC-heparin complex treatment as a necessary prelude to clinical evaluation.
- Development of carbon film composites for use in prosthetic devices.
- Thermodynamic approaches to development and testing of nonthrombogenic materials.
- Basic evaluation of the biocompatibility of materials.
- Use of glow discharge techniques of blood interfaces.

1.3.11 Bio-Instrumentation

The Division of Technological Applications funds and administers a contract supported targeted program in bioinstrumentation which includes an investigation of the acoustic diagnosis of atherosclerosis. Monitoring the developing atherosclerotic lesions is based on the hypothesis that changes in the arterial wall and those imparted to the flowing blood stream by a plaque will alter the acoustic signature generated in a characteristic fashion. Techniques developed for studying incipient failure in artificial devices have been extended to monitoring the state of the cardiovascular system.

1.3.12 Cardiac Diseases--Grant Supported Projects

(Description of this grant supported program is found in Section 1.10.2.)

1.3.13 Cardiovascular Dynamics

This diverse grant supported research area is funded and administered by the Cardiac Functions Branch, DHVD. It contains proposals to do basic research on almost all aspects of the cardiovascular system. While the major focus of this program is "central" cardiovascular dynamics, pertinent to peripheral vascular disease are grants which support projects on: peripheral circulatory dynamics; the function and activities of the microcirculation in providing nutritional blood flow to the tissues and organs of the body; the quantitation of perfusion in collaterial and shunt vessels and their development and contribution in conditions of embarrassed or inadequate local blood supply; rheological properties of blood; the control of the cardiovascular system; and viscosity-reducing blood additives that may be of importance in *in vivo* conditions of turbulent flow, during extracorporeal perfusion or with the use of vascular prosthesis.

1.3.14 Multicategorical Programs

(See Section 1.1.12 for topic description.)

1.3.15 Multiple Risk Factor Intervention Trial

(See Section 1.1.7 for topic description.)

As the ingredients of the "high-risk profile" for peripheral vascular disease are similar to those which predict coronary heart disease, the conduct and results of this trial are applicable to peripheral vascular disease.

1.3.16 Lipid Research Clinics

(See Section 1.1.6 for project description.)

1.3.17 Fundamental Research

(See Section 1.10.4 for topic description.)

1.3.18 Framingham Heart Disease Epidemiology Study

(See Section 1.1.1 for topic description.)

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1.4 HYPERTENSION

1.4.1 Hypertension Detection and Follow-up Program (HDFP)

Funded by contract* and administered by Clinical Applications and Prevention, DHVD, this is a fixed-protocol, controlled clinical trial designed to determine the effectiveness of antihypertensive therapy in reducing morbidity and mortality from hypertension in the general population (including women and younger individuals and many with no target organ disease) and in so doing to: 1) evaluate factors affecting compliance and subset differences in compliance and response to therapeutic measures, and 2) to evaluate the use of paramedical personnel in the follow-up aspects of this program in particular and in clinical trials in general.

In order to obtain statistically significant results of the efficacy of antihypertensive therapy, the HDFP study design determined that a participating population of 10,500-11,000 subjects with elevated blood pressure (diastolic BP≥95mm Hg.) would be required. Fifty percent of this population would be randomized to a "Stepped Care" group (which will receive prescriptions of mild antihypertensive agents initially with more potent agents added, if necessary, in a step-wise manner until the reduced blood pressure goal is reached); the remaining 50 percent would be in the "Regular Care" group (to be referred to the usual sources of care in the community). The goal of treatment is to reduce diastolic pressure 10mm Hg. for those with 95-100mm Hg. and to 90mm Hg. for those above 100mm Hg.

* FY 72: 8 contracts totalling $3,970,833 and 6 contracts extended at no cost.

Phase I of this program involved the structuring of HDFP committees and Policy Board, the development of a standardized fixed protocol, and the carrying out of pilot studies in preparation for Phase II. (Note: Pilot studies have discovered that approximately 15 percent of the total adult participating population had high blood pressure requiring treatment.)

Currently, HDFP has 14 participating clinical centers, a coordinating center, a central laboratory, and an ECG center involved in Phase II which began February 1, 1973. This phase will take approximately 6 years. With the approval and adoption of the protocol and HDFP Manual of Operations, training of individuals in the center staffs, and completion of pilot studies--screening and intake of patients has begun in all HDFP clinical centers. Systematic screening of approximately 150,000 men and women between 30-69 years of age will take place. Those found to have elevated blood pressure will be referred to a specially established hypertension clinic for verification of their blood pressure abnormality. The approximately 10,500 individuals with confirmed elevated blood pressure will be enrolled in this program to determine the degree to which cardiovascular complications and death from hypertension can be reduced by a special management program of antihypertensive therapy--as compared with the "regular" care presently being provided for hypertension.

Phase II will require approximately $7 million for the first year (screening and intake) and approximately $6.6-6.8 million per year for the 5-years of management and follow-up.

1.4.2 Hypertension Specialized Centers of Research (SCOR)

The Hypertension Branch, DHVD, funds and administers the grant supported Hypertension Specialized Centers of Research. (FY 72: five Hypertension SCORs, total funding, $2,495,798--see Table V.)

The intent of the Specialized Centers of Research Program is to focus resources, facilities, and manpower on particular problems in hypertensive diseases and thus to expedite the development and application of new knowledge essential for improved diagnosis, treatment, and prevention of these disorders. The SCORs are designed to emphasize research approaches not "adequately" covered by the research grant, program project grant, or contract supported programs--and when coordinated with these presents a balanced Institute program in hypertension and hypertensive diseases.

These SCORs became fully operational in FY 72. To date, several cooperative arrangements have been made among the centers which, it is anticipated, should promote advances in each. Selected areas of interest and progress include: 1) the selection of specific drugs for hypertension therapy based on plasma renin and aldosterone levels, 2) development, modification of, and improvement in radioimmunoassay methods for angiotensin I and II and aldosterone, making possible more quantitative determinations of these substances in hypertensive patients.

1.4.3 Research and Program Projects--Grant Supported

The Hypertension Branch, DHVD, funds and administers a grant supported program of research in hypertension (i.e., hypertensive vascular disease), renal function and disease, and fluid and electrolyte studies. In FY 72 this program was comprised of 209 grants, totalling $11,826,955--and included six program projects. (Above dollar totals and number of grants do not include Specialized Centers of Research in Hypertension, which are discussed in Section 1.4.2.)

Of this total number of grants approximately 65 percent were for studies on hypertension, 30 percent for renal function and disease, and 5 percent for fluid and electrolyte studies.

In the area of hypertension, the studies cover a broad range of basic and clinical investigations including: analysis of the renin-angiotensin-aldosterone factors in hypertension; a pilot study of mild hypertension in young inner city black females, ages 9-30; and a program project, currently in its 13th year, investigating arterial hypertension, its natural history, complications, and incidence of secondary hypertension (with special reference to renovascular hypertension) in the Black.

Much of the research in grant supported projects in the area of renal disease is concerned with the acquisition of a better understanding of the functioning of the kidney in health and disease. For example, among the NHLI supported projects are several in which renin obtained from the submaxillary salivary gland has been purified and is being studied. Alteration in body fluid compartments as a primary factor in the

hypertensive process and how the kidney responds to or is responsible for these changes is currently being extensively studied. One program project is supported in the area of transplantation--with primary emphasis on the kidney. This group, interestingly enough, can claim the oldest transplanted heart still living (over 4 years) with no rejection episodes during the last year.

Research in the area of fluids and electrolytes is closely related to both hypertension and kidney disease. Some research in this area is a component of many hypertension and/or kidney disease grants--and some reports have indicated that changes in body fluid compartments is of primary pertinence to the development of hypertension.

1.4.4 Clinical Cooperative Study--Treatment of Essential Hypertension

This is a grant supported cooperative, fixed protocol, clinical study. Initiated in 1966*, the study is designed to determine whether the lowering of blood pressure of patients (in USPHS hospitals) with mild to moderate essential hypertension by conventional drug therapy reduces the rate of degenerative complications of the disease. In FY 72, seven grants supported six participating "clinical centers" and a coordinating center, with total funding of $338,981 (see Table VII-A).

* This study succeeded a cooperative study of the treatment of renal hypertension initiated in 1960 to evaluate the relative efficacy of several recognized drug regimens for reduction of blood pressure.

1.4.5 Framingham Heart Disease Epidemiology Study

(See first paragraph from description of this study in the Atherosclerosis section.)

One component project of this longitudinal multifaceted study has been the role of hypertension in the development of congestive heart failure. Another is the elucidation of the natural history of hypertension.

1.4.6 Israel-United States Cooperative Ischemic Heart Disease Study

Administered by the Epidemiology Branch, DHVD, this is an etiology-oriented prospective epidemiological study of hypertension and ischemic heart disease in a defined segment of male government and municipal employees of Israel. (See topic description in Section 1.1.18.)

1.4.7 Epidemiological Investigation of Ischemic Heart Disease and Hypertension in Yugoslavia

Administered by the Epidemiology Branch, DHVD, this P.L. 480 etiology-oriented study is described in Section 1.1.19.

1.4.8 Framingham Offspring Study

(The project is described in Section 1.1.2. Its design and objectives are equally applicable to hypertension as to CHD or atherosclerosis.)

1.4.9 A Twin Study of Genetic Factors in Cardiovascular Diseases

Project description is found under section on atherosclerosis (Section 1.1.14). Project is equally applicable to hypertension.

1.4.10 Bio-Instrumentation

The Division of Technological Applications funds and administers a contract supported targeted program in bio-instrumentation which includes an investigation of the acoustic diagnosis of atherosclerosis--tangentially related to the area of hypertension. Monitoring of developing atherosclerotic lesions is based on the hypothesis that changes in the arterial wall and those imparted to the flowing bloodstream by a plaque will alter the acoustic signature generated in a characteristic fashion. Techniques developed for studying incipient failure in artificial devices have been extended to monitoring the state of the cardiovascular system.

1.4.11 Multicategorical Programs

(See Section 1.1.12 for topic description.)

1.4.12 Behavioral Studies

The Cardiac Functions Branch and the Clinical Cardiac Diseases Branch, DHVD, fund and administer a grant supported research program, the primary objective of which is to

clarify the role of behavioral and environmental factors in the pathogenesis of cardiovascular and pulmonary disease*, but also tangentially related to the area of hypertension.

In line with this, related to hypertension, patients are being taught to voluntarily control systolic blood pressure. While the future application to clinical situations of controlling or preventing hypertension (or arrhythmias or altered vasomotor states) is intriguing, much basic physiologic investigation is still needed.

1.4.13 Cardiovascular Dynamics

This diverse grant supported research area is funded and administered by the Cardiac Functions Branch, DHVD. It contains proposals to do basic research on almost all aspects of the cardiovascular system. While this research area is only tangentially focused on hypertension, pertinent to hypertensive vascular disease are grants which support projects on peripheral circulatory dynamics; the function and activities of the microcirculation in providing nutritional blood flow to the tissues and organs of the body; the quantitation of perfusion in collateral and shunt vessels and their development and contribution in conditions of embarrassed or inadequate local blood supply; rheological properties of blood; the control of the cardiovascular system; and viscosity and drag reducing blood additives that may be of

* The Cardiac Functions Branch is responsible for fundamental studies on operant conditioning and such behavioral studies; on the other hand, the clinically involved topics, such as the control of arrhythmias, are handled by the Clinical Cardiac Diseases Branch.

importance in in vivo conditions of turbulent flow, during extracorporeal perfusion or with the use of vascular prostheses.

1.4.14 Multiple Risk Factor Intervention Trial for the Prevention of Coronary Heart Disease

(See topic description in section on atherosclerosis, Section 1.1.7.)

1.4.15 Honolulu-Hiroshima Study of Coronary Heart Disease and Cerebrovascular Disease

(See topic description in section on atherosclerosis, Section 1.1.16.)

1.5 STROKE

1.5.1 Framingham Heart Disease Epidemiology Study

This multifaceted investigation includes two studies pertinent to the area of stroke: 1) a study of the disability of stroke victims, and 2) an epidemological study of brain infarction associated with occlusive arterial disease. (For topic descriptions see Section 1.2.1.)

1.5.2 Honolulu-Hiroshima Study of Coronary Heart Disease and Cerebrovascular Disease

(See general description of this study in Section 1.1.16.)

All individuals picked up on the screening neurological examination as showing suspicious evidence of cerebrovascular accidents are examined. Findings will be used to determine stroke prevalence in the cohort as well as to eliminate people from the population at risk of developing new stroke.

1.5.3 Israel-United States Cooperative Ischemic Heart Disease Study

This is a prospective epidemiological study of hypertension and ischemic heart disease in a defined segment of male government and municipal employees of Israel. All basic data in this study have been edited and placed on computer tape. A series of tabulations are systematically being produced to look at univariate and multivariate risk factor relationships to incidence of IHD, hypertension, PVD and diabetes--and included is an examination of cerebrovascular accidents.

1.5.4 Joint Study of Extracranial Arterial Occlusion

This effort is an example of grant supported cooperative study in this area.

A cooperative, fixed-protocol, grant supported study designed to investigate obstruction of extracranial arteries supplying the brain as a cause of symptoms of cerebral insufficiency. Surgery is performed on accessible angiographically confirmed lesions--with evaluation of results of surgery (and/or other treatment). This study is in its final stages.

1 5.5 Epidemiology of Atherosclerosis in Evans County, Georgia

This is an example of grant supported projects in atherosclerosis, hypertension, and stroke applicable to this area.

Initiated in 1957 this grant supported epidemiological study on a population of 3,102 residents of Evans County, Georgia, has six documented objectives. Those relating to stroke are as follows:

- To study the incidence and natural history of transient ischemic attacks (TIA) and overt strokes in a prospective fashion.
- To study salt intake and its possible relation to hypertension.
- To evaluate the capacity of certain tests to indicate differences in platelet stickiness between racial and social class groups (as related to physical activity, catecholamines, etc.).

Most of the studies included in this program project conducted since 1958 are clinical and experimental, but there are also epidemiologic studies of hypertension (and its sequelae) and atherosclerosis in black medical and nursing students.

1.5.6 Multicategorical Programs

(See topic description in section on atherosclerosis, Section 1.1.12.)

1.5.7 Cardiovascular Dynamics

This diverse grant supported research area is funded and administered by the Cardiac Functions Branch, DHVD. It contains proposals to do basic research on almost all aspects of the cardiovascular system. Particularly pertinent to cerebrovascular disease are grants which support projects on peripheral circulatory dynamics; the function and activities of the microcirculation in providing nutritional blood flow to the tissues and organs of the body; the quantitation of perfusion in collateral and shunt vessels and their development and contribution in conditions of embarrassed or inadequate local blood supply; rheological properties of blood; the control of the cardiovascular system; and viscosity and drug reducing blood additives that may be of importance in *in vivo* conditions of turbulent flow, during extracorporeal perfusion or with the use of vascular prostheses.

1.5.8 NHLI Hypertension Programs

The documented importance of hypertension as the primary contributor to stroke incidence causes all NHLI program activities in hypertension and hypertensive and renal disease (see section on hypertension) to be pertinent and contributory to Institute activities in stroke.

1.5.9 Fundamental Research--Grant Supported*

(See topic description under cardiac failure, Section 1.10.4.)

1.5.10 Bioinstrumentation

The Arteriosclerosis Branch, DHVD, funds and administers grant supported projects which are involved in the development of safe, sensitive techniques of locating sites of blood vessel obstruction or ruptures. An example of this has been the development of a guided catheter tip. Also, in a broad flow sense, studies are focused upon the development of reliable diagnostic methods for differentiating among various types of strokes.

1.5.11 Thrombosis SCORs

The Division of Blood Diseases and Resources funds and administers a grant supported program of Specialized Centers of Research in Thrombosis. In FY 72 the Institute supported five such SCORs with total funding of $2,106,448. (See Table V.)

The above noted programs relate to the problem of cerebrovascular thrombosis, TIA and stroke. (See Section 3.2.3 for full topic description.)

* Studies in this program area are those involving research which is basic to many areas of the Heart and Lung Institute mission but which have a single discipline approach.

1.5.12 Diagnostic Methods

The Thrombosis and Hemorrhagic Diseases Branch, Division of Blood Diseases and Resources funds and administers a grant-supported program which includes the development of diagnostic methods important clinically for the diagnosis of ongoing intravascular coagulation--and might provide a basis for rational therapeutic measures. (See sections on Blood Diseases.)

1.5.13 Research (Grant Supported) in Atherosclerosis

(See Section 1.1.13 for topic description.)

1.5.14 Joint Study--Aspirin in Cerebral Ischemia

The Division of Heart and Vascular Diseases funds and administers a collaborative study designed to test the protective effect of aspirin in patients who have had episodes of cerebral ischemia associated with occlusive cerebrovascular disease, in situations where surgery would not be appropriate and in certain other well-defined clinical situations where surgery is customary in many institutions.

This is a 5-year term, controlled, double-blind, randomized trial involving approximately 1,000 patients in 10 centers. It is anticipated that a 50 percent or greater reduction may be observed in the frequency of TIA's in ASA (acetylsalicylic acid)-treated patients as compared with controls.
FY 72: One grant totalling approximately $50,000 (this grant supported the study coordinating center). FY 73 finding estimated: Six grants totalling approximately $266,043.

1.6 CONGENITAL HEART DISEASE

1.6.1 Congenital Heart Disease--Research Projects

The Clinical Cardiac Disease Branch, Cardiology, DHVD funds and administers grant supported studies in congenital heart disease (FY 72: 28 grants, totalling $1,870,262--Table I-A). This program area includes the funding of:

- Studies of the etiology, clinical manifestations and epidemiology of congenital heart disease.
- Studies directed toward perfection of existing techniques and the devising of new ones for the repair of defective or diseased hearts.
- Studies directed to the production of new kinds of cardiac valvular prostheses and development of new surgical techniques for their placement or for the repair of damaged heart valves.
- Studies dealing with diagnostic procedures: ECG, body surface mapping; hemodynamics in children and in fetuses; the development and application of new non-invasive diagnostic procedures (e.g., ultrasound); valve motion studies.
- Studies of improved treatment methods.
- A unique canine colony that develops congenital heart disease.
- A limited number of fundamental studies of the chemistry and contractile performance of diseased hearts.

NOTE: The Cardiac Functions Branch funds and administers some fundamental projects on fetal or neonatal development pertinent to the area of congenital heart disease.

1.6.2 Biomaterials

The Biomaterials Branch, Division of Technical Applications, has as one program goal the development of a practical capability to generate a biologically satisfactory blood/artificial device or prosthetic surface interface. The results of activities designed to attain this goal are of import to the continuing refinement of artificial heart valves (which must be constructed of materials that neither affect, nor are affected by, blood and/or tissue and that retain intrinsic qualities of elasticity and strength for years of constant use in such an environment).

Selected projects funded by the Biomaterials Branch pertinent to congenital (and rheumatic) heart disease and the use of artificial heart valves are:

- Development of intimal linings.
- Microfabric substrate development.
- Studies relative to materials suitable for use in artificial hearts.
- Development of blood compatible silicone elastomers.
- *In vivo* screening of potential thrombo resistant materials.
- Polymer studies related to prosthetic cardiac materials which are non-clotting at a blood interface.
- New approaches in the selection of materials compatible with blood.
- The effect of materials on blood leukocytes, erythrocytes and platelets.

1.6.3 Bioinstrumentation

This area is only tangentially related to congenital heart disease. (For topic description, see narrative in section on cardiac failure, Section 1.10.5.)

1.6.4 Cooperative Study of the Natural History of Congenital Cardiac Defects

Started in 1964, this is a grant supported combined retro-active-prospective study of certain common congenital cardiac malformations (ventricular septal defect, valvar aortic stenosis, and valvar pulmonary stenosis) involving a study population of approximately 2,400 individuals. The study is concerned with the development of data on which the prognosis may be predicted for patients with such anomalies in different degrees of severity at different ages and the development of criteria for determining which defects require immediate surgery, which allow postponement of surgery and which can be managed successfully without surgery.

1.6.5 Cardiovascular Dynamics

(For description of this grant supported program, see Section 1.10.3.) It should be noted, however, that this program is only tangentially related to the area of congenital heart disease.

Specific study areas applicable to congenital heart disease include analyses of the dynamic function of the heart in animals and in normal and diseased humans--including active efforts using catheterization procedures, cine-angiography,

video-densitometric techniques, and non-invasive measurements such as the assessment of systolic intervals. The goal of these grant supported studies is to provide safe, reliable procedures for the evaluation of human ventricular performance and to determine appropriate therapy in disease states based on these measurements.

1.6.6 Thrombosis SCORs

(See Section 3.2.3 for full topic discussion.)

The importance, in studies related to congenital heart disease, of development of nonthrombogenic surfaces in artificial heart valves is heightened by the fact that the mitral valve, unlike the aortic valve, is subjected to lower pressures and lower flow velocities. Accordingly, blood clots potentially can form more readily on either valve surfaces or along the line of sutures necessary to position and hold the valve in place. Hence, the research efforts of the Thrombosis and Hemorrhagic Diseases Branch, Division of Blood Diseases and Resources, to further elucidate the mechanism(s) of clotting and the refinement of anticoagulant therapy are of importance.

1.6.7 Research Projects in Thrombosis and Hemorrhagic Diseases

(See sections on Blood Diseases for topic discussion.)

1.6.8 Multicategorical Programs

(See Section 1.1.12 for topic description.)

NHLI

1.7 RHEUMATIC AND OTHER VALVULAR HEART DISEASES

1.7.1 Rheumatic Heart Disease--Research Projects

The Clinical Cardiac Diseases Branch, Cardiology, DHVD, funds and administers grant supported studies in rheumatic heart disease (FY 72: 15 grants, totalling $890,571). This program includes funding of:

- Surgical studies in rheumatic heart disease directed toward perfection of existing techniques and devising new techniques for the repair of the diseased hearts.
- Studies on the production of new kinds of cardiac valvular prostheses and development of new surgical techniques for their placement or for the repair of damaged heart valves.
- Development and application of new non-invasive diagnostic procedures.
- A limited number of fundamental studies of the chemistry and contractile performance of diseased hearts.
- A limited number of fundamental studies of the mechanism of production of rheumatic heart disease by the streptococci.
- Studies of improved treatment methods.

1.7.2 Biomaterials

(See Section 1.6.2 for topic description.)

1.7.3 Bioinstrumentation

This area is only tangentially related to rheumatic heart disease. For topic description see narrative in section on cardiac failure (Section 1.10.5).

1.7.4 Cardiovascular Dynamics

Cardiovascular dynamics studies which involve analyses of the dynamic function of the heart in animals and in normal and diseased humans--including active efforts using catheterization procedures, cine-angiography, video-densitometric techniques, and non-invasive measurements such as the assessment of systolic intervals are tangentially related to the area of rheumatic heart disease. The goal of these grant supported studies is to provide safe, reliable procedures for the evaluation of human ventricular performance and to determine appropriate therapy in disease states based on these measurements.

1.7.5 Multicategorical Programs

(See Section 1.1.12 for topic description.)

1.7.6 Research Projects in Thrombosis and Hemorrhagic Diseases

(See topic description in Blood Diseases Section on thrombosis and hemorrhagic diseases.)

The relation of this effort to rheumatic heart disease: the development of nonthrombogenic surfaces in artificial

heart valves is complemented and supplemented by research efforts supported by the Thrombosis and Hemorrhagic Branch to further elucidate the mechanisms of clotting and the refinement of anticoagulant therapy.

1.8 CARDIOMYOPATHY

1.8.1 Research Projects in Cardiomyopathy

The Clinical Cardiac Disease Branch, DHVD, funds and administers grant supported projects in cardiomyopathy. In FY 72, the Branch funded four projects; total funding was $149,503 (see Table I-A). These projects deal with: 1) The heart in progressive cardiomyopathy; 2) the mechanism of heart failure in myopathic hamsters; 3) behavioral stress in cardiomyopathy; and 4) Chagas' disease in Panama.

1.8.2 Cardiovascular Dynamics

(See Section 1.10.3 for topic description.)

1.8.3 Heart Failure

Cardiology, DHVD, funds and administers grant supported studies in cardiac failure which are also pertinent to aspects of cardiomyopathy:

- Studies of cardiac dilatation and hypertrophy--with ultrastructural correlates--which attempt to explain physiological/ultrastructural derangements.
- Studies of the metabolism of the failing heart.
- Studies of the contractile performance of the failing heart.

1.8.4 Research Projects (Grant Supported) in Cardiac Diseases

(See Section 1.10.10 for topic description.)

1.8.5 Fundamental Research*

(See Section 1.10.4 for topic description.)

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* Studies in this program area are those involving research which is basic to many areas of the Heart and Lung Institute mission but which have a single discipline approach.

1.9 ARRHYTHMIA

1.9.1 Framingham Heart Disease Epidemiology Study

One of the projects supported by this study deals with factors related to suddenness of coronary deaths; another with ECG precursors of sudden death; a third with the evolution of intraventricular conduction disturbances. (See Section 1.2.1 for topic description.)

1.9.2 Research Projects--Cardiac Arrhythmias

In FY 72 the NHLI funded 66 grants totalling $2,637,911 (see Table I) for research in cardiac arrythmias.* This area of grant supported research deals with the processes by which the rate, rhythm, and coordination of cardiac activity are regulated; and with disorders in this system, their nature, manifestations, diagnosis, prevention, control, and treatment.

These research projects in cardiac arrhythmias fall into five categories: 1) diagnostic measurement, 2) instrumentation, 3) assessment and development of drugs, 4) basic studies in cardiac electrophysiology and 5) the role of arrhythmias in sudden cardiac death.

The first category includes: multidisciplinary efforts directed toward multiple electrode body surface mapping, novel analytical approaches in scalar and vector

* These research projects are funded and administered by both the Cardiac Functions Branch and the Clinical Cardiac Diseases Branch depending upon their thrust.

electrocardiography, new studies in magnetocardiography, and direct electrography. Instrumentation involves programs for the design of pacemakers, defibrillators and cardiac resuscitation devices. Studies directed toward cardiac electrophysiology and analysis of the role of arrhythmias in sudden cardiac death serve to elucidate predisposing conditions from which it may be possible to develop methods of prediction, prevention, and treatment. The final area is assessment and development of drugs useful for the treatment and prevention of arrhythmias.

1.9.3 Control of Lethal Arrhythmias Associated with CHD

The Clinical Cardiac Diseases Branch, Cardiology, DHVD, funds and administers seven contracts, totalling $379,970, that deal with studies focused: 1) upon fundamental physiological and biochemical processes and upon interventions which may ultimately lead to clinically applicable techniques, as well as 2) upon clinical approaches which are particularly promising and best suited for evaluation in the clinical setting.

1.9.4 Myocardial Infarction and Sudden Cardiac Death

The Clinical Cardiac Diseases Branch, Cardiology, DHVD, funds and administers studies (FY 72: 15 contracts, totalling $1,701,720) that deal with myocardial infarction and sudden death.

These studies have demonstrated a relationship between arrhythmias and sudden cardiac death (i.e., ventricular fibrillation has been found to be the major cause of sudden cardiac death from two lines of evidence).

Included within these investigations are:

- Studies on early therapy following the onset of symptoms. Recognizing that the majority of patients who die with CHD do so apparently of ventricular irritability and fibrillation in the first minutes and hours after the onset of symptoms, frequently before reaching medical care, a multi-unit study is underway to evaluate the effects of antiarrhythmic agents (lidocaine and atropine) which can be self-administered by a rapidly acting route (five clinics, $77,618).

- A study conducted to evaluate the effects on arrhythmias of prophylactic therapy with anti-arrhythmic drugs.

- A study conducted to evaluate the effect on arrhythmias of coronary artery surgery performed primarily for refractory angina pectoris (this is a collaborative, randomized, controlled study).

- A long-term prospective study of sudden cardiac death, including observation of transient and sustained disorders of cardiac conduction and their relation to increasing the risk of sudden death (and the electrophysiological correlates of risk factors).

- A project which has resulted in the development of computer programs to facilitate large-scale, long-term assessment of cardiac rhythm continuously and of the responses to therapy (these computer programs permit a 60-times real life off-line analysis of ECG records with particular emphasis on variations in QRS morphology).

- A study designed to determine the characterization of electrophysiological and mechanical characteristics of the dog heart during the phase of recovery from regional myocardial ischemia, using this as a model for the pathogenesis of arrhythmias which in humans could lead to sudden cardiac death (the ultimate goal is to design antiarrhythmic interventions to diminish or eliminate the arrhythmias which follow temporary coronary occlusion).

- A study of the relationship of changes in blood pressure and cardiac rhythm in certain phases of sleep to the development of ominous and potentially lethal arrhythmias in persons with coronary disease.

1.9.5 Emergency Medical Services

The Clinical Cardiac Diseases Branch also is involved in funding programs of emergency medical services. The use of specially equipped ambulance systems in three centers has not only provided information on the early pathophysiology of myocardial infarction and sudden death but has demonstrated the feasibility of training paramedical personnel to make significant observations and judgments in cases of cardiovascular emergencies, to obtain EKG signals for transmission, to administer emergency electrical defibrillation, and to administer intramuscular and intravenous medications in addition to the conventional cardiopulmonary resuscitative maneuvers.

1.9.6 Myocardial Infarction Research Units (MIRU)

The Clinical Cardiology Branch, DHVD, funds and administers the contract-supported MIRU program which includes in its investigations and efforts:

- The clinical implementation of automated continuous rhythm analyses and QRS morphology by computer. This is currently being refined and made more feasible for routine clinical monitoring of patients and evaluation of therapeutic interventions.

- Studies which have demonstrated the significance of various arrhythmias and conduction disturbances which occur spontaneously or are induced by intracardiac pacing. From these studies:

  - Has resulted a better description of significant arrhythmias during the acute disease course.

  - Revised indications for long- and short-term intracardiac pacing have been implemented.

- Trials with the pharmacokinetics and clinical effects of antiarrhythmic agents during and after hospitalization.

1.9.7 Cardiovascular Dynamics

(See Section 1.10.3 for topic discussion. It should be noted, however, that the grant supported studies in this area are only tangentially related to the area of arrhythmias.)

1.9.8 Coronary Drug Project

(See Section 1.2.12 for topic discussion.)

1.10 CARDIAC FAILURE

1.10.1 Framingham Heart Disease Epidemiology Study

(See opening paragraph of this topic description in Section 1.1.1.)

This multifaceted study includes two projects directly involved with the area of cardiac failure:

- The Natural History of Congestive Heart Failure. This has been studied over a 16-year period in 5,192 persons initially free of the disease. (Note: Although the usual etiologic precursors have been found, the dominant one is clearly hypertension, which has preceded failure in 75 percent of the cases.) Active production of further reports from follow-up data and from additional analyses is continuing.

- A Collaborative Study of the Efficacy of Systolic Time Intervals in Predicting Congestive Heart Failure. This includes a preliminary analysis of a case-matched control group to ascertain whether the procedure can discriminate persons with an etiology for impaired LV function, but as yet no overt evidence of congestive failure.

1.10.2 Cardiac Failure--Grant Supported Research Projects

In FY 72 the Institute's Clinical Cardiac Diseases and Cardiac Functions Branches supported 68 grants, totalling $2,868,762 (see Table I-A).* This included studies of cardiac hypertrophy, RNA and protein synthesis in the myocardium, the metabolism of the failing heart, the pharmacological action of digitalis and other cardiac glycosides including the metabolism and excretion of these agents, autonomic control and the action

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* Grants are distributed between the two branches according to their thrust.

and metabolism of sympathomimetic amines, contractile performance of the failing centricle, and hemodynamics and venous return in heart failure.

1.10.3 Cardiovascular Dynamics

The Cardiac Functions Branch and the Clinical Cardiac Diseases Branch both fund and administer grants in the area of cardiovascular dynamics that support studies designed to establish explanations for normal function.* These studies, while only tangentially related to the area of "Cardiac Failure," must precede an understanding of disease states, since the information they provide becomes the basis for the formulation of methods of disease detection and diagnosis, and the design of instruments and procedures. They also define the required action of drugs for the prevention, control, and treatment of diseases. This research area interrelates strongly with Institute-supported efforts in cardiac failure as well as other disease specific programs of the Institute.

Examples of the cardiovascular dynamics studies are as follows:

- Basic studies of cardiac biochemistry designed to define the normal biochemical state of the heart and its operation in the absence of pathology.
- Studies on excitation-contraction coupling.
- Studies directed at the analysis of the dynamic function of the heart in animals and in normal and diseased humans (this involves use of catheterization procedures, cine-angiography, video-densitometric techniques, and non-invasive measurements like the assessment of systolic intervals and others) with the ultimate goal: the provision of safe, reliable

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* Grants are distributed between the two branches according to their thrust.

procedures for the evaluation of human ventricular performance; and to determine appropriate therapy in disease states based on these measurements.

- Studies related to the control of the cardiovascular system: neural, hormonal, humoral elements, central vs. local control, and integration of cardiovascular functions.

- Studies of peripheral circulatory dynamics: the function and activities of the microcirculation in providing nutritional blood flow to the tissues and organs of the body; the quantitation of perfusion in collateral and shunt vessels and their development and contribution in conditions of embarrassed or inadequate local blood supply; rheological properties of blood; and viscosity and drag reducing blood additives that may be of importance in in vivo conditions of turbulent flow, during extracorporeal perfusion or with the use of vascular prostheses. (Note: This area of "Cardiovascular Dynamics" is not identical to the category "Fundamental Research.")

1.10.4 Fundamental Research*

Fundamental research is the rubric for a number of grants of a basic science nature, primarily biochemical, which are supportive of many of the NHLI programs. Studies of the biochemical events of muscle contraction, molecular energy production and oxygen-carrying proteins are examples of such fundamental investigations. The relevance of such studies to clinical problems of congestive heart failure, cardiac hypertrophy, and disorders of hemoglobin structure/function is obvious. These studies--previously supported by the Special Programs Branch--are now, following Institute reorganization, supported by the Cardiac Functions Branch.

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* Studies in this program area are those involving research which is basic to many areas of the Heart and Lung Institute mission but which have a single discipline approach.

1.10.5 Bioinstrumentation--Cardiac Failure

The Instrumentation Branch, Division of Technological Applications supports the development and improvement of new or existing blood oxygenators for short-term use in presently existing extracorporeal perfusion systems as supportive mechanisms during open heart surgery for implant of either circulatory assist devices or transplantation in extreme or irreversible cardiac failure. The concepts which have been supported are those which eliminate the blood-air interface (which has been shown to damage blood by denaturation of blood proteins and destruction of cellular elements) and to replace it with a liquid/liquid or a blood-membrane interface.

As the program has progressed, concepts have been supported in which oxygenators have been fabricated from materials that are more thrombo-resistant, and attempts have been made to improve the hemodynamic design of blood oxygenators in an effort to reduce thrombus formation further by eliminating areas of stagnation and turbulent blood flow. In FY 72 efforts have been directed toward developing materials that both meet the specifications with regard to gas transfer and thrombo-resistance and are inexpensive to produce. Emphasis has also been on oxygenator development in:

- Liquid/liquid interface oxygenators.
- Capillary membrane oxygenators.
- Combination pump oxygenators.
- The development of ultrathin membranes.

1.10.6 Biomaterials

The Biomaterials Branch, Division of Technological Applications funds and administers a contract supported targeted program which includes the development of new and improvement of currently used materials for artificial hearts and heart assist devices. (Examples of this effort: studies to develop and apply hydrogel [i.e., non-thrombogenic surfaces] to cardiac assist devices, investigation of electrical and chemical surface and bulk properties of specific polymers to quantitate the degree of thrombogenesis and hemolysis.)

1.10.7 Artificial Devices--Grant Supported

The Clinical Cardiology Branch funds and administers grants that support the development and testing of artificial cardiac support systems. These are grouped under the rubric "artificial devices" program. The program is comprised of a mixture of large program projects and smaller regular research grants. The former are both basic (e.g., theoretical studies of transport and control mechanisms in the cardiovascular system, the development of novel instrumentation methods especially suited to the study of biological materials) and applied (involving the design, implementation, engineering, and physiological study of artificial circulatory assist devices in animals).

This "artificial devices" program of research is applicable to extreme cardiac failure as well as to coronary heart and peripheral vascular disease (see the appropriate sections on coronary heart disease and peripheral vascular disease).

1.10.8 Artificial Devices--Contract Supported

Applicable to irreversible and/or extreme cardiac failure are the targeted, contract supported efforts of the Devices Branch, Division of Technological Applications. The program is divided into four areas: 1) emergency assist devices, 2) temporary assist devices, 3) permanently implantable assist devices, and 4) total heart replacement devices.

The first category includes: intra-aortic balloon pumping devices, mechanical ventricular assistance cups, and external sequenced pulsation (non-invasive) systems--all of which have been developed and currently are undergoing refinement and/or further testing. The second area--temporary assist devices--includes the left ventricular assist pump and bilateral assist system.

In the latter two areas research is being conducted on implanted power for "driving" circulatory assist and/or total heart replacement devices--both nuclear heat source (radioisotope) and electrical energy powered systems have been and are continuing to be investigated. In addition, various engines and prosthetic totally implantable hearts are in different stages of development and/or clinical testing.

A 4-chambered totally implantable heart has been developed and has undergone implantation and testing in animals. Further systems refinement, animal trials, and studies for adaptation to humans are currently being conducted.

1.10.9 Cardiac Transplantation

The Institute supports a small, but broad based, grant funded program in cardiac transplantation comprised of a number of basic and animal studies. The applicability of these studies to irreversible cardiac failure is obvious. Particularly promising are some of the investigations dealing with problems of rejection. For example, studies dealing with the use of irradiation and immunosuppressive agents to "modify" the donor heart indicate a resultant improvement in the survival time of the recipient animal.

NHLI also supports by grant one large program in clinical cardiac transplantation. A small number of highly selected, very carefully studied patients are receiving transplants. This group's survival record has been excellent. Further, important immunological and physiological data is resulting from the study of these patients. This program is, at the same time, pursuing a program in animal transplantation.

1.10.10 Research Projects (Grant-Supported) in Cardiac Diseases

The Division of Heart and Vascular Diseases funds and administers grant supported studies in cardiac diseases having other than ischemic, congenital or rheumatic origins (FY 72: 44 grants, totalling $4,038,829). These studies cover a wide variety of pathological states and include investigations on various forms of cardiomyopathy, diagnostic indices of abnormal cardiac function such as heart sounds and murmurs, and the effects of drugs, toxins, and trace metals on the structure and performance of the heart.

1.11 SHOCK

1.11.1 Research Projects in Shock (Grant Supported)

The Institute in FY 72 supported 50 grants, totalling $2,473,872 (see Table I-A) for research on all forms of shock: hemorrhagic, cardiogenic, traumatic, burn, and septic. Studies are conducted on the mechanisms, treatment, and responses of animals and man to the shock state.

1.11.2 Sequenced Pulsation in Therapy of Cardiogenic Shock

The Devices Branch, Division of Technological Applications, supported, in FY 72, a contract ($47,412) for the development, refinement and testing of a "sequenced pulsation" device, an emergency non-invasive circulatory device for use in therapy of cardiogenic shock. (This device is a compression suit--applied to the lower extremities--by means of which external pressure is applied sequentially from the feet upward during cardiac diastole, producing a counterpulsation wave. Rapid increase of pressure and application of vacuum during isometric systole increases vascular volume and thus reduces left ventricular afterload.)

Tests of this device on human volunteers and on patients undergoing diagnostic cardiac catheterization have concluded.

1.11.3 Myocardial Infarction Research Units (MIRUs)--Studies of Cardiogenic Shock

The MIRU program is funded by contract and administered by the Clinical Cardiology Branch, DHVD. Among the projects

it supports are studies of cardiogenic shock.* These studies include:

- Attempts to automatically control intravascular volume through servo-control mechanisms responsive to the pulmonary artery diastolic pressure. (Note: Continuous monitoring of pulmonary artery pressure and careful regulation of intravascular volume have become standard therapy for patients with heart failure or shock in the MIRUs.)

- An inter-MIRU cooperative trial with the intraaortic counterpulsating balloon assist. (Note: Initial results indicate relative safety of this device and its effectiveness in temporary reversal of the shock state in approximately 75 percent of patients.)

- Pathological correlation of shock (MIRU patients who had cardiogenic shock have consistently demonstrated extensive muscle damage, as well as "shock lesions" in the peri-infarction region. These lesions are not present after reversal of the "shock state" with circulatory assist.)

- Randomized double-blind trials with antiarrhythmic agents.

- Computer applications to hemodynamic monitoring, data acquisition, retrieval, and statistical analysis.

- Patient studies of cardiogenic shock include psychological changes, optimum length of hospital stay, pulmonary ventilation perfusion changes, premature airway closure, changes in pulmonary extravascular water, natural history of unstable angina, and effects of nitroglycerin and bretylium.

1.11.4 Cardiovascular Dynamics

(See Section 1.10.3 for topic description.)

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* One contract: With Massachusetts General Hospital is funded at $713,000.

1.11.5 Research Grants in Cardiac Failure

(See Section 1.10.2 for topic description.)

1.12 NHLI TRAINING

The NHLI has, through its training grants and award programs, attempted to continuously attract a sufficient number of promising young trainees, provide them with high quality training and to encourage the most capable among these inclined toward academic careers to undertake advanced scientific training and supervised research experience. These attempts have focused on an ultimate goal of provision of high quality medical care in sufficient quantity to meet the needs of the patients with cardiovascular, pulmonary, blood and renal diseases. The Institute has attempted to meet these goals through programs providing Undergraduate Training Grants, Graduate Training Grants, Fellowships, Career Development Awards and Pulmonary Academic Awards. (Note: A decision has been made to terminate research training programs of the NHLI Institutes and Research Divisions. This will be accomplished over a phase-out period.)

1.12.1 Undergraduate Training Grants

Undergraduate Training Grants were used to encourage greater emphasis on cardiovascular, cardiorenal and cardiopulmonary diseases at the undergraduate medical student level. Although worthwhile in the past, the decision was made that the primary purpose had been served, and the Institute announced discontinuance of the Undergraduate Training Grants program effective July 1972. In FY 72, the NHLI supported 114 grants in Heart and Blood Vessel Diseases, with total funding of $2,705,648.

1.12.2 Graduate Research Training Programs

The Graduate Training Programs are designed to provide support for the advanced training of physicians and scientists intending to pursue an academic career devoted to fundamental or clinical research or teaching in the general areas of cardiovascular, renal or pulmonary diseases. Grants for this program have been made on a competitive basis to medical schools, universities and other research-educational organizations to assist these institutions in the provision of high quality educational and training opportunities. In FY 72, the NHLI supported 197 graduate research training grants in heart and blood vessel diseases, with total funding of $12,335,331.

1.12.3 Fellowships

The two primary objectives of the Fellowship Program have been: 1) to increase the number of trained cardiovascular and pulmonary investigators and 2) to assure the continuing flow of skilled and imaginative research workers into the cardiovascular, pulmonary and related fields. Promising scientists, selected on a national, competitive basis have received these awards enabling them to obtain advanced scientific training and supervised research experience. These awards have served to encourage the research bent of young persons who show promise of becoming competent research scientists. They have served to provide mature investigators with additional or a specialized research experience and thus to further develop their research skills. In FY 72, the NHLI supported 96 fellowships in heart and blood vessel diseases, with total funding of $831,763.

1.12.4 Career Development Awards

The Career Development Awards Program was designed to provide stable career opportunities for scientists with outstanding potential and competence in cardiovascular, pulmonary or renal research and teaching. This award has carried significant commitments from the Institute for long-term retention of the awardees. In FY 72, the NHLI supported 109 such awards, with total funding of $2,909,195.

SECTION II

LUNG DISEASES

NHLI

II. LUNG DISEASES

Sections 2.1 through 2.15 outline NHLI supported activities correlated with the fifteen (15) major problem areas identified by the Lung Diseases Panel and its supporting task groups. The fifteen areas discussed are:

- The Normal Lung (2.1)
- Environmental Respiratory Diseases (2.2)
- Emphysema and Chronic Bronchitis (2.3)
- Pediatric Obstructive Respiratory Diseases (2.4)
- Allergic Airway Diseases--Asthma (2.5)
- Diffuse Interstitial Respiratory Diseases (2.6)
- Infectious Respiratory Diseases (2.7)
- Sarcoid and Granulomatous Lung Diseases (2.8)
- Hypersensitivity Lung Diseases (2.9)

- Pulmonary Vascular Diseases (2.10)
- Hyaline Membrane Disease of the Newborn (2.11)
- Cystic Fibrosis (2.12)
- Acute and Chronic Respiratory Failure (2.13)
- Extrapulmonary Manifestations of Respiratory Diseases (2.14)
- Education in Lung Diseases (2.15).

2.1 THE NORMAL LUNG

The Division of Lung Diseases funds and administers grant supported fundamental or basic studies of the normal lung. These are conducted as "separate studies" or as component parts of the clinically oriented studies described in other sections. Among these investigations are:

- Studies of the surfactant system in utero (which encompasses a study of all aspects of fetal pulmonary development, as well as a physico-chemical characterization of the components of the surfactant system).

- Studies of carbon monoxide production and body CO stores. These studies have and are elucidating many aspects of carbon monoxide biology and factors involved in oxygen tension in muscle.

- Studies of gas transport in the lung, placenta and tissue with emphasis on further investigation of a transport mechanism present in the alveolar capillary membrane and between cerebrospinal fluid and blood.

- A study of the physiologic relationships of upper and lower airway systems.

2.2 ENVIRONMENTAL RESPIRATORY DISEASES

2.2.1 Noxious Gases

The Division of Lung Diseases funds and administers a grant supported research program on pulmonary effects of noxious gases as environmental pollutants. This research program includes:

- An extensive multidisciplinary approach by one of the Pulmonary SCORs--examining environmental lung disease and oxidant pollutant effects on subcellular and biochemical levels as well as on integrative host responses in animals and man.
- Pathologic studies of the effect of various concentrations of O_3, SO_2, and NO_2 on rat lungs, exposing animals in controlled environmental chambers and then examining the pulmonary lesions.
- Examination of changes in vulnerability to the challenge of infection in pulmonary cells exposed to toxic gases (which may provide concrete data on synergistic effects of pollutants and smoking in diseases such as chronic bronchitis and emphysema.
- Studies designed to construct dose-response data for noxious gas-induced acute bronchioconstriction in animals and man.
- Studies of the effects of acute and chronic exposure to cigarette smoke and automobile exhaust on oxygen transport in the blood, with emphasis on attempts to establish the minimum hemoglobin-carbon monoxide level associated with physiologic and behavioral abnormalities.
- A study of molecular mechanisms of carbon monoxide (and other toxic gas) toxicity.

2.2.2 Inorganic Dusts

The Division of Lung Diseases funds and administers a grant supported research program in inorganic dusts, which covers exposures to mercury, cadmium, asbestos, silica, and coal dusts. This research program includes:

- Studies on cadmium and mercury toxicity, focusing on the elucidation of the mechanism of such toxicity and attempting to distinguish between selective epithelial or capillary damage.
- A prospective survey of asbestos workers and controls (matched for age, years of employment, and smoking habits), seeking to devise methods for early disease detection.
- A Pulmonary SCOR program studying the pulmonary effects of long-term industrial exposure to asbestos, silica, and cement dust.
- A multidisciplinary study of "Black Lung Disease" analyzing aspects of epidemiology, diagnostic criteria, mechanisms of pulmonary injury, pathology, possible treatment and rehabilitation, and methods of dust control.

2.2.3 Organic Dusts

The Division of Lung Diseases funds and administers a grant supported program of research in organic dusts. This research includes:

- A Pulmonary SCOR supported study of cotton dust exposure in cotton workers, emphasizing epidemiological aspects as well as studying the pathophysiology of byssinosis.
- Studies of the immunologic mechanism of Pigeon Breeder's Disease (a hypersensitivity pneumonitis observed in some workers after exposure to inhalation of pigeon feathers or aerosols of droppings).

NHLI

- A study of respiratory reactions in workers exposed to detergent enzymes (which may ultimately define dose-response reactions, natural history information, and provide insights into the pathophysiology of the process).

2.2.4 Tobacco Smoke

The Division of Lung Diseases funds and administers grant supported studies in this area which examine the morphologic pulmonary changes caused by cigarette smoke exposure.

2.2.5 Relationship of the Use of Tobacco to Health

The Epidemiology Branch, Clinical Applications and Prevention funds and administers a continuing study to evaluate the relation of tobacco usage to subsequent mortality.

This is a prospective epidemiolgical study among veterans which monitors smoking habits, respiratory symptoms, and mortality.

2.2.6 The Framingham Heart Disease Epidemiology Study

(See first paragraph in section on atherosclerosis--Section 1.1.1-- for general project description.)

This multifaceted study includes several continuing investigations which have and are documenting the risk factor role that excessive cigarette smoking plays in increasing the chances of developing coronary heart disease.

2.2.7 Multiple Risk Factor Intervention Trial for the Prevention of Coronary Heart Disease

(See section on arteriosclerosis--Section 1.1.7--for description of project.)

This project includes the refinement of current and development of new methods of intervention techniques aimed at reduction or elimination of smoking and will study the efficacy of intervention on this as well as other risk factors in the reduction of incidence of MI and death from CHD over a 6-year study.

2.3 EMPHYSEMA AND CHRONIC BRONCHITIS

2.3.1 Early Diagnosis--Chronic Bronchitis and Emphysema

The Division of Lung Diseases funds and administers grant supported studies in the early diagnosis of chronic bronchitis and emphysema. Among these investigations are:

- A study designed to determine which screening test or combination of tests will best detect early disease. (The study evaluates mechanical properties of the lung with flow-volume curves, correlates these results with diffusing capacity determinations, and uses bronchiography to look at gross airway morphology.)
- A study exploring the possibility of using refined spirometric techniques to measure peak acceleration in early forced expiration as an index of early airway resistance changes.
- A dynamic roentgenographic study with a simultaneous forced vital capacity maneuver (which offers a different method of analyzing air trapping and obstructive phenomena).
- Evaluation of radioactive xenon studies with scintillation cameras are being evaluated in COPD patients in an effort to define early changes in pulmonary perfusion that might characterize the diseases.

2.3.2 Epidemiology and Natural History of Chronic Bronchitis and Emphysema

The Division of Lung Diseases and the Division of Heart and Vascular Diseases fund and administer both grant and contract supported studies in this area. This includes:

- Studies of disease progression in certain clinic patient populations (Pulmonary SCOR, Heart and Vascular Diseases Program Project, pulmonary research grants).

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- Investigations designed to ascertain the prevalence of respiratory disease in certain general populations in this country as well as abroad. This effort includes among its component studies:

  - The US-UK, Norwegian Migrant Study--funded and administered by NHLI--Clinical Applications and Prevention--designed to determine morbidity and mortality from chronic respiratory and cardiovascular diseases among British and Norwegian immigrants in the U.S. and to compare this with analogous data for native born residents of the U.S., Britain and Norway--as part of a larger study to determine reasons for the difference in incidence of these diseases in the three countries.

  - The Epidemiological Investigation of Ischemic Heart Disease and Hypertension in Yugoslavia funded and administered by NHLI-CAP, (see section on arteriosclerosis--Section 1.1.19--for project description)--which includes an investigation of the prevalence, incidence, and etiologic and risk factors in respiratory disease--in particular, but not exclusively, obstructive lung disease. Emphasis is currently given to exploring the relationship of genetic serum α_1-antitrypsin deficiency and obstructive pulmonary disease, particularly pulmonary emphysema.

  - Other studies funded by the Geographical Diseases Section, Epidemiology Branch, Clinical Applications and Prevention (i.e., Israel, Puerto Rico, Honolulu) and Field Epidemiology Section of the same branch (Framingham and Twin Studies).

  - Studies of the effect of recurrent pulmonary infection on the natural history of COPD. These are conducted in both SCOR and research grant supported studies.

2.3.3 Animal Models and Pathogenesis--Emphysema and Chronic Bronchitis

The Division of Lung Diseases funds and administers grant supported studies in this area. Several experimental animal models exist--and permit the evaluation of theories of pathogensis. Among the investigations are the following:

- A proteolytic enzyme, papain, produces an emphysema-like lesion in rats when delivered intratracheally by aerosol. The site and mode of action of this enzyme-induced pulmonary damage is under investigation with attention to the effect of infection on the experimental lesion. This technique provides a model for evaluating structure and function relationships in diseased airways. In the same rats and in controls an NO_2 or SO_2-induced mucus hypersection resembling chronic bronchitis can be produced to study both morphology and physiologic changes. In addition, diffusing capacity determinations supply data on the effect of such papain treatment on the pulmonary capillary bed.

- $Alpha_1$-antitrypsin is known to be an enzyme inhibitor. To explain a chronic obstructive pulmonary lesion associated with a deficiency of this inhibitor, some investigators postulate that the disorder results from unrestrained enzyme action in the lung. Trypsin, collagenase, or elastase administration in sheep provide the means for evaluating such postulates. The studies include aerosol administration and pulmonary artery injection of enzymes in sheep, and attempts in dogs to induce immunologic damage with cellular extracts of proteases. Pulmonary mechanics will be studied in elastin deficient lungs as a possible model for antitrypsin deficiency. Other workers are attempting to isolate and characterize human proteolytic enzymes (including $alpha_1$-antitrypsin) from pancreas, lung sputum, serum, and leukocytes; this may provide further information on the pathogensis of emphysema if the hypothesis of unrestrained enzyme action is true.

- Another animal model for the study of COPD pathogenesis involves rabbits with a pulmonary vascular defect resulting from multiple microemboli. Experimentally this produces a reduction of the pulmonary capillary bed which functionally may be analagous to that seen in human disease.

- An acute pulmonary disorder in mature cattle results from certain changes in feeding regimens. Oral administration of L-tryptophan produces the syndrome experimentally only in cows. Pathologically an emphysema-like destruction of pulmonary parenchyma characterizes the disease. Two studies focus on cause and effect relationships in this disorder at biochemical, physiologic, and microscopic levels.

2.3.4 Mechanics of Breathing--Emphysema and Chronic Bronchitis

Research projects (grant supported) on breathing mechanics relate to the forces and resistances that determine gas flow in and out of the lung. The degree of airway obstruction and the loss of lung recoil, major manifestations in COPD syndromes, are characterized by studies in this area using measurements of airflow resistance, lung compliance, pressure-volume relationships, work of breathing, etc.

During expiratory maneuvers, airflow obstruction is most important clinically and several studies address this problem in considerable detail. Approaches are on several levels ranging from model study to the evaluation of physiologic changes in animals, normal human subjects, and patients with COPD. An investigation of airflow characteristics in collapsible tubes uses a physical experimental model to evaluate mathematical predictions for airflow compression. Flow limitation studies in animals will hopefully give insight into mechanisms operating in humans with disease. Small

"retrograde" catheters pulled through the airways have been used to determine the contribution of different sized airways to flow resistance. In vivo physiology studies with follow-up pathologic data and in vitro studies of diseased airways followed by detailed pathologic analysis allow structure and function correlations in the problem of airway compression. At the tissue level, mechanical properties in excised samples of lung can be studied in normal and disease states.

An investigation carefully describing respiratory mechanics in COPD patients during exercise may suggest therapeutic interventions to improve exercise tolerance in these patients. With exercise, COPD patients may experience dyspnea or breathlessness at levels of work much less than that tolerated by normal subjects. The mechanism of dyspnea is the central focus of several studies directed at elucidating external load perception during ventilation in normal patients and in disease states. This may provide insight into factors controlling ventilation during breathlessness.

Other studies related to breathing mechanics concern an analysis of regional lung expansion as a function of inspired volume using radioactive xenon, an evaluation of the effects of anesthesia, and a study of comparative mammalian respiratory mechanics.

2.2 ENVIRONMENTAL RESPIRATORY DISEASES

2.2.A Environmental Respiratory Diseases--Department of Agriculture

The USDA funds and administers or conducts research related to this area (FY 72: six projects, no funding data available).

The projects conducted are:

- Tobacco Smoke Constituents and Ultrastructural Cell Changes in Tracheal Tissue. The objective of this study is to develop a new bioassay method based on ultrastructural cell changes in tracheal tissue of rodents brought about by tobacco smoke constituents.
- Effect of Cigarette Smoke on the Respiratory Epithelial Cell Turnover Rates in Mice. The objective of this study is to develop a new bioassay method based on respiratory epithelial cell turnover rates in mice.
- Effect of Tobacco Smoke on Lipid Uptake in Animal Tissue. The objective of this study is to develop a new bioassay method based on the effect of tobacco smoke on lipid uptake in animal tissue.
- Effect of Tobacco Smoke Components on Chromosomal Aberrations of Rodents. The objective of this study is to develop a rapid bioassay procedure based upon the effects of tobacco smoke constituents on chromosomes, tissues, and organs following oral and intravenous administration.

2.2.B Environmental Respiratory Diseases--Atomic Energy Commission

The AEC funds and administers studies in the area of environmental respiratory diseases (FY 72: four onsite contracts, totalling $3,745,000; two offsite contracts, totalling $54,000).

- A broad program of research on the toxicity of inhaled environmental toxicants, particularly radioactive materials, is conducted at the Lovelace Foundation, Pacific Northwest Laboratory, and University of Rochester. In these studies, beagle dogs and rodents are exposed to graded doses of radioactive aerosols in order to define and quantitate long-term effects of radiation in the lungs and other organ systems (including spatial and temporal aspects of the radiation response). The metabolism of soluble and insoluble radioactive aerosols is investigated to elucidate the relative sensitivity of lung, lymph nodes, liver, and bone to protracted but changing dose rates. Data from long-term studies of these sorts are required for the formulation of meaningful radiation protection guides. These data also serve as a basis for the evaluation of biological consequences associated with occupational and population exposures to man-made radiation. At the present time, low doses of alpha-emitting radionuclides are of particular interest. Mechanisms of pulmonary injury as well as the early detection of pathologic changes in the lungs are investigated as part of the overall effort. Therapeutic measures (lung lavage, chelate therapy, and stimulation of phagocytic activity) designed to reduce body burdens of radionuclides are also being developed. It is worthy of note that research at the Pacific Northwest Laboratory includes the study of combined effects produced by the inhalation of radioactive aerosols and chemical toxicants (cigarette smoke, carnotite ore, benzpyrene, chrysotile asbestos, and diesel fuel). Research conducted at two AEC (onsite) facilities on the uranium miner problem, which is a part of the inhalation radiotoxicology program, is facilitated by support from NIEHS (FY 72: one contract at the Pacific Northwest Laboratory, $350,000; one contract at the University of Rochester, $51,000).

- At the Los Alamos Scientific Laboratory, a different exposure technique is employed in the study of pulmonary effects produced by alpha radiation. Plutonium-containing microspheres are administered intravenously to Syrian hamsters in such a way that the particles lodge in the pulmonary microvasculature. The immobilized particles cause a protracted exposure of lung tissues to alpha radiation.

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2.3.8 Connective Tissue--Emphysema and Chronic Bronchitis

Grant supported studies of the chemistry of connective tissue remodeling are being conducted to improve our understanding of disease mechanisms in the emphysema-predominant type of COPD where the disease may be characterized by a structural failure of collagen fibers. Little is known about the age-related and disease-related changes in lung elastin and the sites of origin and effects of pulmonary enzymes with collagenolytic or elastolytic activities. In other grant supported studies the development of tissue culture techniques for propagating pulmonary cells *in vitro* provides an exciting tool for the investigation of these synthetic processes in the lung.

2.3.9 Rehabilitation and Treatment--Emphysema and Chronic Bronchitis

The Division of Lung Diseases funds and administers grant supported studies in this area.

Therapy in COPD is largely supportive and directed at symptomatic relief, although more attention is now being placed on rehabilitation of the pulmonary cripple. Several studies attempt to delineate responses to exercise in normal subjects and in patients with COPD in hopes of applying new principles of exercise tolerance to retraining and rehabilitation. Results are still equivocal as to whether carefully graded exercise actually delays progression of the disease. As one of its efforts, one of the Pulmonary SCORs is involved in the development of instrumentation to evaluate therapeutic regimens and to conduct critical studies of their effectiveness.

A relatively new area of program support in COPD rehabilitation involves studies of the psychological and psychosocial aspects of patients with COPD. Useful information will hopefully accrue in regard to patient understanding of the disease, the prognosis and disability.

2.3.10 Bronchiectasis

The Division of Lung Diseases funds and administers grant supported studies in this area.

In the current program, a long-term study of the natural history of the disease in 26 patients with proven bronchiectasis has already shown that these patients now die more frequently from cardiovascular deaths than from severe infection. Studies of tracheobronchial clearance and ventilation-perfusion distribution, in addition to routine pulmonary function testing and bacteriologic studies continue in an effort to plot the course of the disease. Unilateral lung lavage has been applied therapeutically with temporary improvement in lung function.

2.3.11 Bullous Disease

The Division of Lung Diseases currently funds and administers one grant supported study relating to this disease. It focuses on long-term follow-up of patients who have had surgery for bullous disease.

2.4 PEDIATRIC OBSTRUCTIVE RESPIRATORY DISEASES

2.4.1 Specialized Centers of Research in Pulmonary Disease

The Division of Lung Diseases funds and administers grant supported Pulmonary Specialized Centers of Research (FY 72: 17 Pulmonary SCOR's, total funding; $6,467,151--See Table V).

The intent of the Pulmonary Specialized Centers of Research program is to focus resources, facilities, and manpower on particular problems in pulmonary diseases and thus to expedite the development and application of new knowledge essential for improved diagnosis, treatment, and prevention of these disorders. The SCORs are designed to emphasize research approaches not "adequately" covered by the research grant, program project grant, or contract supported programs--and when coordinated with these presents a balanced Institute program in pulmonary disease.

Viral bronchiolitis is under study in several SCORs. One project focuses on the development of an animal model of adenovirus bronchiolitis, while another is examining the natural history of such an illness in children with special attention to the possible development of chronic pulmonary disease.

2.4.2 Research Grants

The Division of Lung Diseases funds and administers grant supported studies in the area of viral bronchiolitis. One such study involves the attempt to develop a live, attenuated viral vaccine for direct intratracheal instillation in viral bronchiolitis.

2.5 ALLERGIC AIRWAY DISEASES--ASTHMA

2.5.1 Asthma

While work on the immunologic and allergic bases of asthma is the province of other Institutes, the NHLI Lung Program funds and administers grant supported studies dealing with this disease in regard to pulmonary functional impairment (FY 72: seven grants, totalling $340,602).

Studies examining the associated physiologic changes in respiratory parameters in acute asthmatic attacks are conducted in Pulmonary SCOR's program project and research grant supported investigations. Also conducted in SCOR and research grant supported investigations are studies--in asthmatics with irritable airways--of the possible interaction between directly inhaled antigenic stimuli to bronchiospasm and the non-antigenic stimuli such as SO_2 pollution. The pharmacologic mediators of bronchiospasm (histamine, SRS-A, etc.) are also being evaluated.

Research grant-funded basic physiologic studies in asthmatic patients between attacks seek to separate this group from patients with chronic bronchitis and emphysema on the basis of elastic lung recoil and diffusing capacity characteristics. However, other investigators are conducting studies--supported by program project--on the natural history of asthma in order to examine the possibility that patients with spasmodic asthma may ultimately develop a COPD-like disease.

The possibility of behavior conditioning control of respiratory resistance in asthmatics is the focus of a project in a new SCOR program, where the biochemical bases of asthma are also being investigated. Investigations on lung innervation are designed to contribute to a better understanding of neural control of bronchoconstriction and ultimately, rational pharmacologic therapy.

Bronchopulmonary lavage, now applied as a therapeutic measure in some resistant asthmatic attacks, is being evaluated for more precise clinical indication for therapy and with attention to associated changes in mechanics, gas exchange, and blood flow.

2.6 DIFFUSE INTERSTITIAL RESPIRATORY DISEASES

2.6.1 Diffuse Pulmonary Fibrosis

The Division of Lung Diseases funds and administers grant supported studies in this area (FY 72: six grants, totalling $424,751).

One project attempts to evaluate possible treatment modalities in a radiation-induced diffuse pulmonary fibrosis in dogs. Steroids and triiodothyronine are used and studies also include pathologic and electron microscopic analysis in an attempt to delineate whether epithelial or endothelial damage initiates the syndrome. Such studies are of importance since radiation-induced pulmonary lesions are a potential hazard in numerous patients receiving X-ray therapy for pulmonary neoplasms. Thus, limits and mechanisms of toxicity must be defined.

A study of patients with pulmonary fibrosis utilizes multidisciplinary techniques to define the etiology of the individual cases with the help of lung biopsy and pathologic analysis and to decipher the pathogenic mechanisms leading to these changes. Simultaneously, laboratory investigations study the various hypotheses regarding the role of physical, chemical, immunological, and microbial insults in the pathogenesis and progression of the disease. Detailed pathologic studies will be correlated with tissue, cellular and molecular reactions.

Contributions to the understanding of basic mechanisms in pulmonary fibrotic reactions should result. A SCOR program also focuses on pathologic changes in chronic interstitial

pneumonias with a continuing registry of morphologic data in addition to physiologic and clinical information on patients with diffuse fibrosis.

Another program is now evaluating animal models of diffuse alveolar injury and fibrosis with an emphasis on structure-function correlations. This study will also include detailed morphologic study of the diseased lung in addition to organotypic culture techniques.

2.7 INFECTIOUS RESPIRATORY DISEASES

2.7.1 Infectious Pneumonitis

The Division of Lung Diseases funds and administers grant supported studies* in infectious pneumonitis, with specific interest in the way in which such diseases affect pulmonary function, complicate the course of chronic pulmonary disease, and are predisposed to by underlying pulmonary impairment.

These investigations include:

- Studies of the relationship of pulmonary infection to the pathogenesis of COPD and bronchiectasis.
- Studies of ciliary clearance as a defense mechanism against pathologic insults from infectious agents.
- A longitudinal study on interactions of organisms in the nasopharynx of children, attempting to determine whether specific respiratory disease syndromes exist which require the presence of two or more microbial agents and to what extent secondary infection complicates disease being caused by a single microbial agent.
- A study of the natural history of adenovirus bronchiolitis in children, with special attention to the possible development of chronic pulmonary disease.

* Table IB shows for FY 72 one grant at $41,740; however, this refers to grants with total or major emphasis. In FY 72, seven grants (including three SCORs) supported, as part of their investigations, studies of infectious pneumonitis.

- A study focusing on the development of an animal model of adenovirus bronchiolitis.
- A longitudinal study of desquamative interstitial pneumonitis.

2.8 SARCOID AND GRANULOMATOUS LUNG DISEASES

2.8.1 Sarcoid Lung Diseases

The Division of Lung Diseases funds and administers grant supported studies in this area (FY 72: six grants, totalling $288,030).

In the current Division of Lung Diseases program, work in progress addresses several aspects of the disease. One project involves the analysis of the biochemical basis of the Kveim tissue reaction which is used as a diagnostic test in sarcoid. Other workers and one SCOR program provide attention to problems of pathophysiology with research on an experimental granulomatous lesion similar to sarcoid. Using this disease model in dogs, they attempt to evaluate the time course of changes in gas exchange impairment during the development of the experimental granulomatous disease.

Several projects study diffusion impairment in sarcoidosis.* The effect of short versus prolonged therapy with steroids on this parameter and on lung volumes will be studied in an effort to determine whether physiologic indices and the natural history of the disease change favorably with such treatment.

* This effort includes a contract supported study funded and administered by the Division of Technological Applications (Project title: Fabricate Optimized Templates and Study Blood Flow Through a Short Path Membrane Blood Oxygenator).

Several projects include the longitudinal evaluation of groups of sarcoid patients. The information accruing from these studies will ultimately contribute to our understanding of the natural history of the disease.

2.9 HYPERSENSITIVITY LUNG DISEASES

2.9.1 Allergic Interstitial Pneumonitis

Allergic diseases, as in the case of infectious diseases, are the province of other Institutes in regard to the immunologic mechanisms of pathogenesis. However, these reactions are also of interest to the NHLI when they affect the lung. The Division of Lung Diseases funds and administers a program of grant supported studies in this area (FY 72: six grants, totalling $1,028,955).

Allergic hypersensitivity reactions in the lung resulting in diffuse pneumonitis are caused by various extrinsic agents, usually by inhalation exposure as in Pigeon Breeder's Disease or in allergic aspergillosis. Precipitating antibodies are seen in the serum and the etiology of these diseases is quite likely immunologic. Investigations in this area are discussed separately in the section on inhalational exposures. Also supported is a new multicenter, multidisciplinary approach to "farmer's lung" allergic interstitial pneumonitis. This program includes extensive epidemiologic, etiologic, immunologic, physiologic and pathologic studies of hypersensitivity pneumonitides in man and on animal models.

Several other studies seek to elucidate the mechanism of immunologic reaction that leads to pulmonary injury. Such work may also help to explain pathogenic mechanism of pulmonary injury in other diseases where underlying immune injury is suspected but not yet proven, as in the auto-immune phenomena postulated for collagen vascular diseases.

2.10 PULMONARY VASCULAR DISEASE

2.10.1 Cor Pulmonale

The Division of Lung Diseases funds and administers grant supported studies in the area of cor pulmonale (FY 72: seven grants, totalling $135,785).

Pulmonary hypertension produces right heart strain which can lead to right ventricular hypertrophy. When right ventricular hypertrophy results strictly from pleuropulmonary disease rather than secondary to left ventricular failure or valvular disease, the situation is called cor pulmonale. Chronic bronchitis and emphysema are frequent causative factors in this syndrome. When the syndrome is obvious clinically, these patients are often in the preterminal stages of their disease. In general, right heart failure is an ominous sign in these diseases.

One study is evaluating the use of vectorcardiography for the diagnosis of right heart strain. Vectorcardiographic strain may provide an easily detected index of early disease in this syndrome and may also be a useful tool for following the course of chronic cor pulmonale.

Experimentally producing pulmonary hypertension and cor pulmonale in dogs, another program seeks to study the hypotheses that right ventricular dysfunction secondary to the destruction of the pulmonary vascular bed may be a significant factor limiting the physiologic performance of patients with COPD. Basic physiologic studies in animals on the relationship between right heart function and the

pulmonary circulation, and on the site of pulmonary vascular resistances may contribute to the understanding of the disease process in man.

2.10.2 Pulmonary Edema

Pulmonary edema can be a catastrophic and life-threatening situation arising from any disturbance in the normal balance of forces that keep the alveoli dry. Increased pulmonary venous pressure secondary to left ventricular failure or valvular heart disease is probably one of the most common factors, but direct changes in alveolar-capillary membrane permeability characteristics play a role as well. Toxic or allergic insults to these membranes (e.g., heavy metals, heroin, respectively) are thought to act in this way. The study of the pathophysiology of pulmonary edema and the therapy which best supports these patients is very important, since there can be considerable mortality in the untreated state.

The Division of Lung Diseases funds and administers grant supported studies in this are (FY 72: 15 grants, totalling $562,520). This program of research includes:

- Several basic physiologic projects, one of which focuses on the alveolar-capillary membrane studying flows (water, solute, current) and forces (hydrostatic pressure, osmotic pressure, and electric potential) across these membranes in isolated animal lungs. Other studies involve evaluation of the application of trans-thoracic electrical impedence measurements as a diagnostic tool in the assessment of pulmonary edema and other changes in cardiopulmonary function.

- Pathophysiologic studies of pulmonary edema, in which non-invasive indicator dilution techniques are used

to study organ blood flow in human subjects with special emphasis on changes in capillary volume and extravascular water. Other projects deal with the effect of respiratory mechanics in the development and prevention of pulmonary edema.

- While the forces involved in the formation of lung edema are well elucidated, the routes by which exudate is absorbed from alveoli have yet to be analyzed quantitatively. This is an important pathophysiologic aspect of pulmonary edema and present work on the relative role of blood and lymph in protein removal from alveoli should contribute useful information. Additional insight into the mechanisms and pathways of pulmonary lymphatics will accrue from an electron microscopic analysis of lungs in dogs with chronic pulmonary edema.

- Various substances can produce a toxic reaction in the lung leading to pulmonary edema. Dogs subjected to repeated exposure to Alloxan develop an interstitial edema presumably on the basis of endothelial leakage. This process results in fibrin formation and serves as a model for studying this type of pulmonary edema as well as the role of fibrin in its formation and resolution.

- The use of intravenous heroin sometimes results in a toxic or perhaps allergic type of pulmonary edema. Studies which attempt to characterize the mechanism of this reaction are supported, as are studies of the therapeutic mechanism of morphine.

- Pulmonary edema occurs occasionally during exertion at high altitude in natives who have temporarily been at sea level or in unacclimatized subjects. Left ventricular failure does not contribute to this condition. A physiologic study in dogs is attempting to elucidate the mechanisms producing this abnormality and hopefully will contribute information with therapeutic implications for this problem.

- Increased intracranial pressure has been shown to cause reflex changes in the pulmonary circulation that can lead to edema formation in the lungs. Several projects focus on the mechanisms that control these changes. This work may provide information for the therapeutic support of patients with head trauma or intracranial lesions.

2.10.3 Pulmonary Hypertension

Pulmonary hypertension can develop in otherwise normal subjects and can severely complicate the course of disease states such as emphysema and chronic bronchitis, cystic fibrosis, kyphoscoliosis, and pneumonia. When it leads to right-sided heart failure in these conditions, therapeutic intervention often provides little effect.

The Division of Lung Diseases funds and administers grant supported studies in this area (FY 72: 17 grants, totalling $649,336).

Basic to investigation in this disease category, is the study of acute and chronic mechanisms of pulmonary hypertensive changes. If the mechanisms are better elucidated, then appropriate pharmacologic therapy may follow.

Altitude studies presently supported provide a unique opportunity for studying this problem in that pulmonary hypertension exists in altitude dwellers independent of pulmonary parenchymal disease or cardiac disease. With the variable of underlying disease processes removed, investigators may and are focusing on the physiologic consequences of an abnormally high pulmonary perfusion pressure on blood oxygenation and ventilation-perfusion imbalance. Such work may determine whether or not the physiologic results of pulmonary hypertension represent useful adaptation to disease stress. In the situation where primary pulmonary disease (e.g., COPD, etc.) produces pulmonary hypertension, it is possible that the resultant physiologic change actually improves ventilation-perfusion distribution, albeit at the expense of increased strain on the right side of the heart.

Other work at altitude seeks to investigate changes in acid-base balance or electrolytes that might effect blood coagulability, pulmonary vasomotor responses or peripheral chemoroceptors and contribute to pulmonary hypertension through these means.

Animal models are useful in this area of study. In certain cattle at altitude, a syndrome of acute pulmonary hypertension and right heart failure develops (Brisket Disease). Physiologic studies in these animals have been conducted. In the young pig, pulmonary hypertension develops at altitude or after ligation of a single pulmonary artery. Studies with this model now continue at sea level attempting to demonstrate similar changes with acute hypoxia independent of altitude.

Another animal model involves intravenous administration of mucin in the young calf. This has been shown to produce pulmonary hypertension that can be blocked by pre-treatment with oxygen or aspirin. It is hypothesized that the mucin or a released substance is involved in an oxygen-dependent regulation of the pulmonary circulation. Intravenous amniotic fluid also produces pulmonary hypertension in cows. The mechanism of this reaction is also being studied.

The lung contains various vasoactive substances that might mediate such reactions and may play an as yet unexplained role in pulmonary hypertension. Other workers are now focusing on the study of location, metabolism, and action of these vasoactive substances in the lung. The role of

human circulating fibrinopeptides in experimental pulmonary hypertension is also being studied.

Pulmonary hypertension frequently complicates cardiac disease. In congenital heart defects where large pulmonary flows develop as a result of left-to-right shunting, pulmonary vascular disease is a chief cause of failure in corrective surgery or of inoperability. In an effort to delineate the optimum age for operability, investigators are studying both the pathogenesis and the basic mechanisms involved in pulmonary hypertension related to congenital and surgically produced cardiac lesions.

2.11 HYALINE MEMBRANE DISEASE OF THE NEWBORN

2.11.1 Neonatal Respiratory Distress Syndrome

The Division of Lung Diseases funds and administers grant supported studies in the area of neonatal RDS (FY 72: 11 grants, totalling $1,444,648).

Hyaline membrane disease or idiopathic respiratory distress of the newborn may account for as many as 20 percent of all neonatal deaths in this country. Yearly mortality is estimated at approximately 25,000 but the exact incidence is actually unknown. While certain risk factors such as prematurity and Caesarian section are now known to be associated with an increased incidence of the disease; the exact pathogenesis is yet to be elucidated. Furthermore, considerable debate exists on techniques of therapeutic intervention with these infants.

The addition of the pulmonary Specialized Centers of Research (SCOR) grants in June 1970, greatly expanded the NHLI Division of Lung Diseases effort in neonatal RDS. Two of the centers devote all of their resources to multidisciplinary investigations of hyaline membrane disease. In combination with other SCOR grants and regular research grants, these projects result in a broad-based program addressing issues of etiology, pathophysiology, pathology, treatment, sequelae, and possible methods of prevention.

Longitudinal studies of neonatal RDS will add important information on the natural history of the disease. Projects

in this area now include joint efforts by obstetricians, anesthesiologists, and pediatricians and will ultimately help describe relevant events in the antenatal, labor and delivery, newborn and extended follow-up periods.

Studies of fetal development may provide insight into etiologic factors in neonatal RDS. One project is designed to address fetal steroid and lipid biosynthesis and metabolism during pregnancy and parturition and to coordinate these studies with other biochemical and anatomical analyses in the developing lung. This work may provide some physiologic basis towards understanding the risk of prematurity and its relationship to hyaline membrane disease.

One study uses animal models (lambs) to examine possible pathogenic factors such as intrauterine stress, hypovolemia, and bleeding diseases with reference to physiological, biochemical, and pathological consequences.

Correlations between neonatal RDS and deficiency in serum enzyme inhibitors have been made and work continues in this area with special focus on $alpha_1$ globulin and $alpha_2$ globulin levels.

The study of fetal and neonatal pulmonary circulation may also provide data on pathogenesis. The possible association of neonatal RDS and patent ductus arteriosus is being studied.

Several animal models allow excellent opportunity to study the factors that produce both the normal increased pulmonary vascular resistance in the fetus and the pathologic continuance in the neonate. Using intrauterine and exteriorized

fetus preparations in the goat and lamb, investigators are examining pulmonary vascular responses to hypoxia, hypercapnia, change in pH and vasoactive drugs while attempting to localize the site of the vascular resistance. The effect of human fibrinopeptides on pulmonary vasoconstriction will also be evaluated as a possible contributing factor in the pathogenesis of this disease. In addition, the program contains studies of the forces governing fluid transudation in lungs of immature lambs with RDS.

As in the case of adult RDS research programs, efforts are now being made to develop new and improved methods of monitoring patients in neonatal intensive care units. Such computer-assisted monitoring systems will help establish the principles under which RDS infants may be optimally ventilated and will offer a sophisticated method of analyzing the effect of therapeutic maneuvers.

Projects relating to management and treatment of infants with RDS include evaluation of limited extracorporeal membrane oxygenation, studies of the use of end-expiratory positive pressure versus continuous external negative pressure ventilation and the effects of total parenteral alimentation on recovery rates and growth patterns in RDS infants. Special ventilatory equipment for infants and children with RDS is being developed, and the effect of exchange transfusion on pulmonary function is being evaluated.

2.12 CYSTIC FIBROSIS

2.12.1 Cystic Fibrosis--Grant Supported Studies

The Division of Lung Diseases funds and administers grant supported studies in cystic fibrosis and other genetic lung diseases (FY 72: four grants, totalling $101,144). These studies are supported through SCOR and research grant mechanisms and include:

- Comprehensive evaluation of cardiac and pulmonary function--and the natural history of their decline or improvement with therapy.
- Studies using pulmonary function tests, including flow volume analysis of mechanical impairment to help evaluate therapeutic interventions such as antibiotics, bronchiodilators, or mucolytic agents.
- Biochemical studies of the mucous abnormality in cystic fibrosis.

2.12.2 Alpha$_1$-Antitrypsin Studies

The Division of Lung Diseases funds and administers a contract supported program of alpha$_1$-antitrypsin studies applicable to cystic fibrosis and other genetic lung diseases (FY 72: seven contracts, totalling $368,685).

This program of studies includes:

- An investigation of familial occurrence of alpha$_1$-antitrypsin, COPD, and their interrelationship.
- An investigation designed to determine the importance of genetic factors in predisposing to COPD and the importance of alpha$_1$-antitrypsin deficiency in their genetic predisposition.

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- An investigation designed to establish the prevalence of heterozygous alpha$_1$-antitrypsin deficiency and the various Pi genotypes in patients with emphysema.

- An attempt to develop new and original approaches to the diagnosis of heterozygous alpha$_1$-antitrypsin deficiency.

2.13 ACUTE AND CHRONIC RESPIRATORY FAILURE

2.13.1 Respiratory Distress Syndrome: Post Traumatic RDS--Adult

The Division of Lung Diseases funds and administers a grant supported program in this area, encompassing projects related to early diagnosis, pathophysiology, and treatment. This program includes:

- A study of the time-course of the development of RDS manifestations should provide useful information on the natural history of the acute disease. Investigation of this kind may provide clues for early diagnostic changes in ventilatory pattern and other parameters of disturbed pulmonary physiology such as mechanics, blood gases, etc. Computer interpretation with on-line direct readout of various physiologic parameters will facilitate the evaluation for possible predictive diagnosis before the full-blown syndrome develops; the effect of therapy may also be closely followed. This technology has now been applied in ongoing studies to continuous measurements of physiologic parameters such as ventilation-perfusion relationships, alveolar-arterial oxygen gradients, continuous blood gas determination, and diffusion and measurement of lung water.

- The effect of various anesthetic agents, muscle relaxants, and types of mechanical ventilators on pulmonary mechanics and the distribution of ventilation and perfusion is being studied. One project focuses on the effect of anesthesia-related and experimental postoperative atelectasis, the time course of its development, and the efficacy of various methods of therapy.

- Acute RDS caused by smoke inhalation and thermal injury is also being studied in the current program. This work seeks to determine the relative roles of heat, particulate matter, irritating gases, and steam in the production of the acute pulmonary complications.

2.13.2 Membrane Oxygenators and Ventilatory Assistance

The development and evaluation of respirators and oxygenators is essential to improving therapeutic intervention in RDS affecting all age groups. In these patients, hypoxemia may be great and lung injury or infection so extensive that extracorporeal oxygenation offers the only viable means of temporary support.

The Division of Lung Diseases funds and administers a program of grant supported research in this area. (It should be noted that the bulk of the research effort is a contract program funded and administered by the Division of Technological Applications--see pertinent topic discussion.)

The Division of Lung Diseases grant supported program includes in its investigations:

- Studies to develop a non-clotting membrane interface.
- Long-term studies of the physiologic effects of available oxygenators in animals.
- Limited clinical studies with humans of short-term oxygenator support.
- Studies of physiological and technological problems of liquid breathing systems for acute support of patients with RDS-related hypoxemia.

2.13.3 Membrane Oxygenators and Ventilatory Assistance--Contract Supported Studies

The Division of Technological Applications funds and administers a contract supported program for the development

and improvement of new or improved blood oxygenators. This program includes:

- Studies addressing the development of a non-clotting membrane interface--and its testing *in vivo* for its effects on blood elements.
- The development of an improved pump oxygenator.
- Studies of fabrication problems in membrane oxygenator devices and heart devices.
- Development of special bioinstrumentation to detect incipient failure in devices and to monitor pump blood pressures and oxygenation.
- Testing and evaluation effort of available oxygenators.

2.13.4 Oxygen Toxicity

Prolonged exposure to 100 percent oxygen or to oxygen-enriched mixtures of inspired gas is known to produce pulmonary damage. The mechanism of this pulmonary oxygen toxicity is as yet unknown. It is frequently seen in adult acute RDS or in neonates where severe hypoxemia and pulmonary shunting require high oxygen concentrations to sustain adequate levels of tissue oxygenation.

The Division of Lung Diseases funds and administers a program of grant and contract supported studies in this area. Two large program projects with multiple subprojects deal completely with research related to oxygenation problems, oxygen effects and multidisciplinary approaches to the therapeutic and complicating features of hyperbaric oxygenation. The respiratory projects in most of these programs are generally concerned with a quantitative determination of tolerance

limits to high oxygen exposures. Other investigations now focus both on the basic mechanisms involved in pulmonary damage as well as the study of possible adaptive processes in this kind of exposure.

In animal models, changes in cell biochemical and metabolic pathways, abnormalities of cell division, and electron microscopic evaluation of pathologic tissues will be studied at varying oxygen exposures in grant and contract supported studies. The possible protective action of such substances as glutamine, glutamate, GABA, or succinate will be evaluated in pathologic studies of mammalian liver, brain, lung, and kidney after hyperoxic exposure. Monkey models are being evaluated with the goal of developing time-pressure tolerance curves using pathology as an end point in dose-response measurement.

The possibility of increased susceptibility to pulmonary infection is the focus of several studies. One deals with the possible activation of latent pulmonary virus infection and on the effect of infectious challenge in animals exposed to hyperoxic environments. Defense mechanisms may be damaged, thus reducing the normal protective action of mucus clearance and the function of alveolar macrophages.

The therapeutic efficacy of continuous positive pressure breathing will be examined since atelectasis and alveolar collapse may play a role in the pathogenesis of oxygen toxicity.

Toxic oxygen damage to other tissues such as those in the central nervous system may be related to pulmonary injury.

NHLI

Oxygen convulsions are the focus of one project while the possibility of reflex neurogenic influence or endocrine organ effect on pulmonary pathology are also being studied.

2.14 EXTRAPULMONARY MANIFESTATIONS OF RESPIRATORY DISEASES

2.14.1 Control of Ventilation

The Division of Lung Diseases funds and administers grant supported studies which deal with the mechanisms which mediate ventilatory changes in response to chemical alterations in the blood (PO_2, PCO_2, pH). These investigations include:

- One project addressing the central issue of whether chronic hypoxia itself decreases the ventilatory response to hypoxia. Using isocapneic hypoxic ventilatory studies performed with rebreathing techniques, investigators are comparing ventilatory responses of normal subjects and those with reversible lung disease to patients with chronic lung disease and hypoxia.

- Studies which examine the relationship of ventilatory drives to added external resistive and elastic loads in order to determine whether mechanical problems contribute to the lack of appropriate ventilatory responses. The converse is also being studied by investigators examining the effect of increased ventilation (produced by hypoxia or hypercarbia) on pulmonary mechanics.

- Studies which seek to separate and quantitate the effects of humoral and neural components in the control of pulmonary ventilation.

- Examination of the contribution to total chemical ventilatory drive of the carotid and aortic bodies in animal models, normal subjects, and in patients with reduced ventilatory response to PCO_2.

- Exercise studies in normal subjects and in patients with chronic lung disease.

- Studies in animal models of the responses to and recovery from severe hypoxia--with special focus on the survival value of sympatho-adrenal and ventilatory responses.

- Studies of drugs that affect the hypoxic or hypercephalic ventilatory drive patterns (which has application to possible therapeutic ventilatory stimulation in patients with a blunted response).

2.14.2 Control of Circulation

The Division of Lung Diseases funds and administers grant supported studies of the cardiac and pulmonary manifestations of reflex changes in the circulatory system produced by acute and chronic hypoxemia. Investigations in this area are useful in several ways: data on basic physiologic regulatory mechanisms result from studies of hypoxic effects on the pulmonary circulation; inferences as to the adaptative usefulness or maladaptive nature of these physiologic mechanisms may be made; a more rational approach to management and therapy may be planned.

These investigations include the following studies:

- Several projects which utilize the stress of hypoxia as a tool towards understanding the basic physiology of the pulmonary circulation. (Note: In most studies other factors are used as well. For example, in unanesthetized dogs with chronically implanted recording catheters, investigators are studying pulmonary arterial tone regulation and the effects of hypoxia, adrenergic blockade, and denervation.)

- Several projects which deal with the distribution of perfusion and its alteration in shock and in hypoxic states. In both acute and chronic states, radioisotope scanning allows relatively noninvasive procedures for human studies and animal experimentation.

- While most studies dealing with the distribution of perfusion in hypoxic states work with whole animal or whole lung preparations, one project attempts to resolve changes at the microcirculation level.

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(Using high speed movies at high magnification, pleural surface pulmonary arteries, capillaries, and veins are being studied with the goal of determining whether generalized whole animal hypoxia causes different changes in the microvascular bed than does localized hypoxia confined to the region of lung under direct observation).

- Studies designed to determine if chronic hypoxemia alters the functional capacity of the cardiovascular system.

- Studies of isolated pulmonary vascular strips to examine the relationships between oxygen tension, contractility, and cellular metabolism.

2.14.3 Oxygen Transport

The Division on Heart and Vascular Diseases funds and administers grant supported studies in the area of oxygen transport. These investigations include:

- Studies on cellular adaptations to chronic hypoxemia or chronic hypercapnia--specifically focusing on changes in cell metabolism and biochemistry, and intracellular acid-base changes.

- Studies of the controls and interactions of all factors intervening in the physiologic compensation for hypoxia.

- Studies of the relationship of factors such as the Bohr effect and the intra-erythrocyte compound 2,3 diphosphoglycerate which displace the oxyhemoglobin dissociation curve and affect hemoglobin binding of oxygen.

2.15 EDUCATION IN LUNG DISEASES*

2.15.1 Graduate Research Training Programs

The NHLI Graduate Training Programs are designed to provide support for the advanced training of physicians and scientists intending to pursue an academic career devoted to fundamental or clinical research or teaching in the general areas of cardiovascular, renal or pulmonary diseases. Grants for this program have been made on a competitive basis to medical schools, universities and other research-educational organizations to assist these institutions in the provision of high quality educational and training opportunities. In the area of lung diseases, in FY 72, 40 of these awards were made totalling $2,800,000.

2.15.2 Fellowships

Two primary objectives of the NHLI Fellowship Program have been 1) to increase the number of trained cardiovascular and pulmonary investigators and 2) to assure the continuing flow of skilled and imaginative research workers into the cardiovascular, pulmonary and related fields. Promising scientists, selected on a national competitive basis, have received these awards enabling them to obtain advanced scientific training and supervised research experience. These awards have served to encourage the research bent of young

* A decision has been made to terminate research training programs of the NIH Institutes and Research Divisions. This will be accomplished over a phaseout period.

persons who have shown promise of becoming competent scientists. They serve to provide mature investigators with additional or a specialized research experience and thus further develop their research skills. In the area of lung diseases, in FY 72, 18 fellowships were given totalling $166,000.

2.15.3 Career Development Awards

The Career Development Awards Program was designed to provide stable career opportunities for scientists with outstanding potential and competence in cardiovascular, pulmonary or renal research teaching. This award has carried significant commitments from the Institution for long-term retention of the awardees. In the area of lung diseases, in FY 72, 29 of these awards were given totalling $751,000.

2.15.4 Pulmonary Academic Awards Program

This award was designed to develop and/or extend pulmonary programs in schools of medicine or osteopathy and at the same time to provide financial support, encouragement and opportunities for academic career growth for the young physician or scientist interested in pulmonary disease. Each eligible institution could nominate one candidate for the award who would be an individual interested in devoting a major portion of his time to the development of a pulmonary curriculum and the inclusion of teaching methods in this area. The award was made for a 5-year period and was renewable for a maximum of 3 years. Table IV-C shows that in FY 72, there were 16 Pulmonary Academic Awards, totalling $727,790.

SECTION III

BLOOD DISEASES

III. BLOOD DISEASES

Sections 3.1 through 3.7 outline NHLI supported programs correlated with seven (7) major problem areas as delineated by the Blood Diseases Panel and its task groups. The seven areas discussed are:

- Hemophilia and Other Bleeding Disorders (3.1)
- Arterial Thromboembolism (3.2)
- Disorders of Hemostasis Due to Platelet Abnormalities (3.3)
- Venous Thrombosis and Pulmonary Embolism (3.4)
- Thromboembolism in Relation to Prosthetic Devices (3.5)
- Microcirculatory Thrombosis (3.6)
- Hemoglobinopathies (3.7).

Following this discussion is a statement on training grants and awards in the area of Blood Diseases (3.8).

3.1 HEMOPHILIA AND OTHER BLEEDING DISORDERS

3.1.1 Hemophilia and Other Bleeding Disorders--Non-Targeted Research

The Thrombosis and Hemorrhagic Diseases Branch, DBDR, funds and administers a grant supported program of research in hemophilia and other bleeding disorders (FY 72: 11 grants, totalling $823,994*).

The overall objectives of this research program are: a better understanding of the physiologic mechanisms of hemostasis, of the pathologic derangement of these mechanisms that result in hemorrhagic diseases, the development of tests for the early and accurate diagnosis of the disorders and the development of tools for their prevention and therapy.

A significant number of the grants supported are involved in a broad range of fundamental studies directed at an understanding of the complex mechanisms that promote coagulation and clot lysis, with a view of better understanding the diseases resulting from blood factor deficiencies. Efforts in this area include such studies on the plasma coagulation factors as: the genetic and physiologic mechanisms that control their production; sites of formation at organ, cellular and molecular levels; and the nature and mechanisms of activity of a variety of coagulation factors and inhibitors.

* Note: FY 72 NHLI annual report shows 33 grants in the area of hemophilia with total funding in excess of $1,500,000. The totals shown above represent grants with major emphasis in hemophilia and other bleeding diseases; the remainder have a less significant emphasis in this area.

In addition, studies are carried out on the mechanism of joint destruction in hemophilia with efforts to find further approaches to suppress this damage. Purification and testing of plasma fractions in the development of therapeutic preparations is also carried out. Other research in this area involves studies of the complement system as it relates to hemostasis, inheritance pattern of bleeding abnormalities and the biochemical, morphologic and functional aspects of platelets in Von Willebrand's disease.

3.1.2 Hemophilia and Component Therapy

The Blood Resources Branch funds and administers a contract supported targeted program dealing with hemophilia and component therapy (FY 72: eight contracts totalling $445,077).

The program supports efforts in two areas: 1) standardization of cryoprecipitate and 2) platelet preservation. In the former, studies are focused upon the definition of a standard process for producing cryoprecipitated factor VIII which would ensure the highest yield per unit of blood. In the area of platelet preservation, studies are directed toward the development of techniques to increase the *in vivo* lifespan of platelets (without loss of clinical effectiveness). The importance of this to the problem of preservation of platelets for transfusion to thrombocytopenic patients is self-evident.

3.1.3 Specialized Centers of Research in Thrombosis

(See Section 3.2.3 for topic description.)

3.2 ARTERIAL THROMBOEMBOLISM

3.2.1 Arterial Thromboembolism--Non-Targeted Research

The Division of Blood Diseases and Resources funds and administers a grant supported program of research in arterial thromboembolism (FY 72: 36 grants, totalling $2,445,681--see Table I-C).

The grants in this area primarily support basic studies necessary to the understanding of the underlying causes of thromboembolism and the interaction of blood and its constituents with the arterial vessel wall or its substitute (i.e., prosthesis). (Note: The application of knowledge derived from these studies is often funded by programs of other divisions of the Heart and Lung Institute and by other institutes, e.g., investigations involving thrombosis as specifically affecting the various organs of the body--heart, lung, kidney, brain, etc.--and its prevention, diagnosis, and treatment as related to the organ or prosthesis.)

Basic research projects employ multiple disciplines through the involvement of biochemical, physiologic, pathological, immunological, molecular, genetic, biophysical and therapeutic fields. Fundamental as well as some clinical investigations relevant to the prevertion of pending coagulation problems and diagnosis of the early or completed thrombotic process include work on platelets, plasma factors, fibrin and thrombin and their precursors, inhibitors and activators, and many other blood and vessel wall components as well. Some promising assays based on fibrin degradation products are being developed along with tagging and scanning techniques, thus providing

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potential tools for the prevention and quantitation of the intravascular coagulation process and the localization and extent of accomplished thrombosis. In vitro and in vivo models are being developed to study the cellular, chemical and hemodynamic variables in the production of thrombi and to test drugs and chemicals potentially able to prevent thrombosis or to lyse formed thrombi.

In the area of treatment, a number of anticoagulation and clot lysis agents are undergoing intensive study and when proven efficacious and relatively safe, carefully controlled clinical trials are initiated. Some of the better known are heparin, warfarin, urokinase, streptokinase, etc. Searches are also being made for synthetic fibrinolytic/thrombolytic preparations.

Because of their importance to the advance of the thrombosis and related fields, conferences on timely topics are also supported. For example, the III International Congress on Thrombosis and Hemostasis was recently held in Washington, D.C., providing a forum for discussion of thrombosis as a world health problem. A second conference supported by this grant supported program focused on clot stabilizing enzymes--which have a central role in hemostasis and wound healing. (Preliminary experiments have indicated that the clot stabilizing enzyme is the only factor affected by estrogen and progesterone, thus suggesting that an increase of this enzyme might be responsible for the thrombotic state. This is especially relevant to the question of contraceptive pills.)

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3.2.2 Clinical Trials of Thrombolytic Agents in Acute Myocardial Infarction

Recognizing the importance of congestive heart failure and cardiogenic shock as contributors to mortality from acute myocardial infarction, the Blood Resource Branch in FY 71 and 72 funded and administered a contract supported program designed to evaluate the role of thrombolytic agents in salvaging ischemic myocardial tissue in acute myocardial infarction.

Results of pilot studies*, along with data from European trials led the Institute to issue an RFP soliciting proposals from prospective clinical centers, and an RFP to solicit proposals for a coordinating center which together will undertake a full scale controlled clinical trial. Currently, proposals submitted in response to both RFPs are undergoing review.

3.2.3 Specialized Centers of Research in Thrombosis

The Thrombosis and Hemorrhagic Diseases Branch, DBDR, funds and administers grant supported Specialized Centers of Research in Thrombosis (FY 72: five SCOR grants, totalling $2,106,448).

The intent of the Specialized Centers of Research program is to focus resources, facilities, and manpower on particular programs in thrombosis and hemorrhagic diseases and thus to expedite the development and application of new knowledge essential for improved diagnosis, treatment, and prevention of these disorders. The SCORs are designed to emphasize research approaches not "adequately" covered by the research grant, program project grant, or contract supported programs--

* The studies have been concluded. (FY 72: one interagency agreement, totalling $66,480)

and when coordinated with these presents a balanced Institute program in thrombosis and hemorrhagic diseases.

Examples from among the many areas of interest are: 1) the study of inhibition and reversal of platelet aggregation, 2) the study of the activity of cell and vessel membranes by ultra-microscopy, and 3) the isolation and characterization of coagulation factors XI and XII.

3.3 DISORDERS OF HEMOSTASIS DUE TO PLATELET ABNORMALITIES

3.3.1 Hemorrhagic Disorders Due to Platelet Abnormalities

The Thrombosis and Hemorrhagic Diseases Branch funds and administers a grant supported program of research in hemorrhagic disorders due to platelet abnormalities (FY 72: 13 grants, totalling $546,689).

The objectives of this research program are to further clarify the nature of the platelet abnormalities in patients with defects in the primary arrest of bleeding (thrombocytopenia, thrombasthenia and Von Willebrand's disease). To this end studies directed toward the elucidation of the mechanisms and control of platelet contraction, adhesion, aggregation and release, crucial for normal hemostasis, are carried out. Furthermore the physicochemical, metabolic and biochemical bases for platelet coagulant activity, such as contact product forming activity, collagen-induced coagulant activity, intrinsic factor X_a-forming activity, platelet factor III activity, antiheparin activity, and platelet factor IV activity are studied as well as their possible importance and significance in the pathogenesis of thrombosis. Efforts in this area include such studies as the biochemical and physiological properties of subcellular platelet compartments, platelet energy metabolism, membrane phosphorylation and regulation of platelet function, molecular biology of platelet-platelet and platelet-endothelial interactions, adenosine metabolism and the interaction of platelet receptors with adenylate cyclase, formation and release of prostaglandins in

human platelets, platelet contractile protein and collagen-platelet interaction. In addition, studies are carried out on the mechanism whereby immune complexes attach to platelet membranes and the role of complement in the production of platelet injury.

3.4 VENOUS THROMBOSIS AND PULMONARY EMBOLISM

3.4.1 Venous Thrombosis and Pulmonary Embolism--Non-Targeted Research

The Thrombosis and Hemorrhagic Diseases Branch, DBDR, funds and administers a grant supported program of research in venous thrombosis and pulmonary embolism (FY 72: 24 grants, totalling $993,882).

While the grants in this area are heavily clinical, the research program also includes basic studies conducted in several animal species. The objective of these investigations is to understand the underlying mechanisms contributing to the initiation and pathogenesis of venous thromboembolism phenomena and their prevention, diagnosis and treatment.

Epidemiologic studies on prevalence and incidence of venous thrombosis are being supported. In addition, investigations are proceeding to assess the risk factors associated with the complications of venous disease (post-phlebitic syndrome and pulmonary embolism) in high-risk, hospitalized patients where frequency of venous disease complications are greater than usual. The classical concept of venous thrombosis being a stasis clot is being challenged, resulting in investigations of the value of agents affecting platelet function in reducing the risk of thromboembolism in patients according to the effect on the biochemistry and aggregation of platelets and the interaction of platelets with surfaces and participation of platelets in thrombotic disease. It is anticipated that a controlled clinical trial with agents affecting platelet function will result in a prophylactic method of treating complications which is less hazardous than anticoagulant therapy.

Methods presently used or being evaluated for the diagnosis of venous thrombosis include the clinical examination, venography, Doppler ultrasound technique, impedance plethysmography, radioactive scanning techniques, and various coagulation assays. All are being improved or refined, and a series of sensitive assays and diagnostic tests are being developed to detect the presence, location and severity of thrombus formation and to aid in the prevention and treatment of thromboembolic disease and its complications.

Basic and applied studies in animals are exploring: the role of the endothelium in the initiation of thrombosis and fibrinolysis employing mechanical injury and serum injection; the changes produced by oral contraceptives in the surface charge density of vessel walls and blood cells utilizing electrokinetic methods; the role of intravascular fibrin formation and deposition, and mechanisms involved relating to venous thrombosis and certain other clinical states; changes that occur in the coagulation system, platelets and fibrinolytic system before and during experimental formation of thrombi; the value of a variety of assays, proposed to undergo change during thrombosis, in detecting the early thrombotic state; the thrombogenic effect of histamine and other substances liberated from the mast cell on veins utilizing light and electron microscopy, autoradiography, chemical and coagulation tests; the intravasation of marrow fat and pulmonary fat embolism after bone marrow injury; and the role of various agents on the genesis of venous thrombosis and the efficacy of pharmacologic agents in preventing or alleviating venous thrombosis.

3.4.2 Urokinase-Streptokinase Pulmonary Embolism Trial

The Blood Resources Branch funds and administers this cooperative clinical trial composed of two phases:

- Phase I--designed to measure primarily the thrombolytic capacity and possible therapeutic benefits of urokinase (a common thrombolytic agent). Principal results of this phase of the trial have been published --demonstrating that the urokinase and subsequent heparin regimen significantly accelerated clot resolution as evidenced by angiograms, photoscans, and hemodynamic measurements.

- Phase II--designed to compare the thrombolytic capacity and toxicity of urokinase and streptokinase (another common thrombolytic agent). This involves patients receiving a 12- or 24-hour regimen soon after suffering pulmonary embolism. All patients receive subsequent heparin.

In FY 72, nine contracts, totalling $251,667, were funded.*

3.4.3 Nonurinary Urokinase

The Blood Resources Branch funds and administers a contract supported program of studies designed to explore the possibility of obtaining urokinase from non-urinary sources--which would ensure the availability of an enlarged inexpensive supply of urokinase for exploration of the drug's efficacy in thromboembolic diseases.

To date, urokinase-producing cultures have been established, and the urokinase harvested from these cultures is being purified and tested to ensure a clinically safe and useful product. In FY 72, two contracts, totalling $374,363, were funded.

* does not include carry-over from FY 71 funding.

3.4.4 Specialized Centers of Research in Thrombosis

(See Section 3.2.3 for topic description.)

3.5 THROMBOEMBOLISM IN RELATION TO PROSTHETIC DEVICES

3.5.1 Thromboembolism in Relation to Prosthetic Devices

At present, the Division of Blood Diseases and Resources supports no major project in this area.

3.5.2 Biomaterials

The Biomaterials Branch, Division of Technological Applications, has as one of its program objectives the development of surface which can simulate the characteristics of the intimal lining of the human cardiovascular system. This involves the formation of a contiguous lining of cells which are nonthrombogenic, tightly adherent to the wall lining of a flexible surface, self-replicating and immunologically unrecognizable to the host's own tissues.

Further description of this topic and examples of studies supported are listed in the section on Peripheral Vascular Disease, Heart and Blood Vessel Diseases.

3.6 MICROCIRCULATORY THROMBOSIS

3.6.1 Microcirculatory Thrombosis--Non-Targeted Research

The Thrombosis and Hemorrhagic Diseases Branch, DBDR, funds and administers grant supported research in microcirculatory thrombosis (FY 72: three grants, totalling $418,334--Table I-C).

Through the integrated application of techniques in biochemistry, physiology, and light and electron microscopy, *in vivo* and *in vitro* investigations are being conducted on blood platelets, red blood cells, the vessel wall and the lung, including basic work on cells, membranes and the microvascular system in animals and applied work in humans. The organs studied in normal humans and patients dying of shock and pulmonary edema are gastrointestinal tract, lung, kidney, myocardium, brain and extremities. Advanced and promising quantitative procedures are being applied to the study of mechanisms of platelet and fibrin thromboembolism, as well as hemostatic reactions in the living blood vessels of the microvascular system. Studies are being pursued to determine what biophysical and biochemical changes occur during thromboembolism and hemostasis. Special attention is given to the reaction of platelets both *in vivo* and *in vitro* and attempts made to counteract or minimize the deleterious effects caused by the defense mechanisms normally utilized by the body to compensate for injury of the vascular system.

3.6.2 Specialized Centers of Research in Thrombosis

(See Section 3.2.3 for topic description.)

3.7 HEMOGLOBINOPATHIES

3.7.1 Hemoglobinopathies--Non-Targeted Research

The Thrombosis and Hemorrhagic Diseases Branch funds and administers a grant supported program of research in hemoglobinopathies (FY 72: 113 grants, totalling $9,498,960). These grants support primarily fundamental research directed toward a better understanding of red blood cell energy metabolism and the oxygen-carrying capacity of hemoglobin, particularly related to the elucidation of the pathogenesis of various anemias and polycythemia.

These studies fall into four major categories: 1) red blood cell metabolism; 2) erythrocyte membrane structure and permeability; 3) red blood cell production (erythropoiesis); and 4) hemoglobin synthesis, structure and function.

Studies dealing with red blood cell metabolism involve the metabolic properties of red blood cells which contribute to their viability and which support their physiological function in the circulation: i.e., protein and lipid synthesis, oxygen transport properties, regulation of glucose metabolism, glycolysis and energy metabolism. Also involved are studies of cellular physical properties such as deformability, adhesiveness, motility and viscosity; physicochemical factors involved in the interaction of blood cells with one another and with their suspending medium; and the determination and investigation of biochemical, clinical, hematological and genetic parameters in hereditary diseases in which an inborn error is demonstrable in the metabolism of red blood cells. Studies dealing with erythrocyte membranes involve studies of active

transport across cell membranes, the relationship of their chemical properties and function to cell types, transition from fetal to adult characteristics of membrane transport, effect of various agents and conditions on anion permeability, the relationship of various components of the cell in defining the structure of the membrane and of various enzymatic activities in influencing their physiological and biochemical behavior, and the relation of pyridine nucleotides to membrane transport and permeability. Studies dealing with red blood cell production are directed at achieving a more precise understanding of the factors involved in the control of erythropoiesis in man--and determining the potential role of humoral factors in treatment of selected types of anemia. Tissue cultures are being developed for the production of erythropoietin.

Radioimmunoassay methods are being developed for erythropoietin to assist in the identification of cellular sites of its production. Purification of erythropoietin for its assessment in clinical anemia and polycythemia is underway. Also involved are studies of the biogenesis of erythropoiesis stimulating factor, its ultrastructural site and biochemical mode of action. The erythropoietic inhibitory factor present in the plasma of polycythemia patients is also being investigated. Studies of hemoglobin are essentially directed toward the elucidation of the relationship between structure and function, and the regulation and control of hemoglobin synthesis. These involve genetic regulation of hemoglobin synthesis, X-ray crystallography, amino acid sequence determination, allosteric properties, the Bohr effect, hemoglobin subunit associations including heme-heme and heme-protein

interactions, reaction of hemoglobin with ligands and antibodies and the relationship of ligand binding and confirmational changes in hemoglobin.

3.7.2 Studies in Sickle Cell Disease

The Sickle Cell Disease Branch funds and administers a contract supported, mission oriented research and development program--which has as one of its objectives the study of mechanisms for the prevention and treatment of sickle cell disease. The contract supported studies in sickle cell disease (FY 72: 27 contracts, totalling $1,662,715) involve investigations of the pathophysiological mechanisms involved in precipitating the sickling event--and investigations of cell energetics, transport kinetics, and membrane lipid metabolism of the sickle cell disease red blood cell under various conditions. The studies are addressing such issues as:

- What are the properties of sickle hemoglobin and of sickle hemoglobin-containing erythrocytes which may be involved in the sickling process, and what mechanisms are effective in preventing and/or reversing sickling?
- What are the biochemical and physiological characteristics of the irreversibly sickled, the reversibly sickled, and the non-sickled erythrocyte from the homozygous S patient, and what do modifications of the hemoglobin molecule do to these characteristics (e.g., cell energetics, transport kinetics, and membrane lipid metabolism)?
- How do these cells function outside the patient (in vitro or in an animal model) in terms of flow characteristics, survival, and oxygen delivery?

- How do these cells function in the patient in terms of flow characteristics (e.g., conjunctival flow studies, thermography, washout studies, and scans), survival, and oxygen delivery (e.g., Hickam-Frayser technique for measuring flow and O_2 consumption in the retina)?

- Can tissue damage and/or destruction and its progression be measured (e.g., by use of radioactive scans, enzyme studies, etc.) in the sickle cell disease patient?

- Is there derangement of the coagulation-fibrinolytic system in the sickle cell disease patient, both in and out of crisis?

- Is there derangement of the white blood cell or other component in the immune mechanism in the sickle cell disease patient?

3.7.3 Clinical Trials of Therapeutic Approaches to Sickle Cell Crisis

The Sickle Cell Disease Branch funds and administers contract supported collaborative clinical trials of therapy for sickle cell vaso-occlusive crisis. These trials are part of the Branch's mission-oriented research and development program.

Three trials (FY 72: seven contracts, totalling $643,117) are presently being conducted:

- A randomized, modified double-blind, clinical trial investigating the efficacy of low dose urea therapy as compared to alkalinization, hydration and electrolyte therapy.

- A controlled, modified double-blind, randomized trial comparing the efficacy of high dose urea therapy with hydration and electrolyte therapy.

- A controlled, modified double-blind, randomized trial comparing intravenous alkalinization versus hydration and electrolyte therapy.

3.7.4 Prenatal Diagnosis of Inherited Hematologic Diseases

The Blood Resources Branch funds and administers a contract supported program of research in the prenatal diagnosis of inherited disease. While the prime focus of this effort has to date been sickle cell disease, this program of research will also include hemophilia. Both direct and indirect (genetic linkage) approaches have been investigated. To date, excellent progress has been made toward the production of goat antiserum specific for hemoglobin S. Also the synthesis of Beta-globin chains has been unequivocally demonstrated in reticulocytes of the end-trimester human fetus. Genetic linkage studies are proceeding well and it is anticipated that present efforts will lead shortly to the perfection of a safe means of *in utero* fetal visualization. (FY 72, four contracts, totalling approximately $192,700.)

3.7.5 Sickle Cell Disease Centers

The Sickle Cell Disease Branch funds and administers a grant supported program of Sickle Cell Disease Centers. In FY 72 the Branch supported 10 such centers, with total funding of $4,860,000.

The purpose of the Sickle Cell Disease Centers is to focus resources, facilities, and manpower in a coordinated approach to sickle cell disease. This approach includes a combination of research and service with the intent of bridging the gap

between these two disciplines. Programs of the Sickle Cell Disease Centers include basic or fundamental research, clinical research, clinical applications, treatment trials, training and education programs, public education, screening, counselling, rehabilitation, and related activities. Research in progress, at the present time, includes molecular studies, cellular studies, organ studies, flow studies, and studies in coagulation and immune mechanisms as they apply to sickle cell disease.

3.7.6 Sickle Cell Screening and Education Clinics

The Sickle Cell Disease Branch funds and the Health Services and Mental Health Administration administers a grant supported program of screening and education clinics established as demonstration projects to determine the best ways to carry out programs of public awareness, public education, screening, counseling and patient referral. The intent of these programs is that of obtaining data to find out how best to carry out these program components in a variety of environments and under certain conditions.

In FY 72 the Branch supported 19 such clinics with total funding of $1,900,000.

3.7.7 Sickle Cell Disease Research Project Grants

The Sickle Cell Disease Branch funds and administers a program of investigator initiated research under the grant support mechanism. In FY 72, the Branch supported nine such grants, with total funding of approximately $300,000. These investigations include studies such as:

- Microcirculation in sickle cell anemia--an animal model
- Binding of small molecules to sickle hemoglobin

- Translational control of protein synthesis
- Physical chemistry of human hemoproteins
- Factors controlling expression of erythropoietic sites
- Biochemical approaches to sickle cell anemia
- Role of cysteine residues in hemoglobins A.F. and S
- Investigations of rigid hemoglobin syndromes.

(Note: In addition, a Sickle Cell Disease Information Program is underway to assemble and disseminate information through various means to the public on sickle cell disease.)

3.7.8 Thalassemia (Cooley's Anemia)

In FY 72, there were no NHLI grant or contract programs limited solely to Cooley's Anemia although research on this disease is part of the programs listed below. The figures given represent the amount of the total award. It was not possible to assign a dollar figure to the fraction of effort related to Cooley's Anemia in each grant.

- Inhomogeneity of Hemoglobin and Myoglobin Types. This grant supported research is concerned with the molecular pathology of human hemoglobin variants and of other hemoglobinopathies. Emphasis is placed on studies concerning the relation between functional (and clinical) symptoms and abnormal properties due to alterations in structure. In addition, the importance of some new genetic developments, notably those concerning the multiplicity of hemoglobin structural genes and the existence of silent structural genes is being further evaluated--so that a better insight into the genetic basis of inherited hematological disorders, in general, and the various forms of thalassemia, in particular, may be obtained (FY 72: $71,598).
- Abnormal Hemoglobin Syndrome. This investigation involves a study of the pathophysiology and biochemistry of abnormal hemoglobin syndromes. Specifically: 1) a study seeking biological, physiological, and clinical explanations for the variability between

subjects who seem to have the same sickling syndromes, 2) a study seeking to explain anemia despite only mild hemolysis in hemoglobin C disorders, 3) a study seeking reasons for a mild homozygous thalassemia syndrome seen predominately in Blacks, and 4) a study attempting to modify with treatment (e.g., urea) the clinical course of the sickling disorders (FY 72: $18,082).

- Expansion of Research Facilities in a Hematologic Center. A program project providing support for the maintenance and expansion of core facilities in a hematologic research center--which in its research scope conducts investigations on abnormal hemoglobins and thalassemia (FY 72: $78,232).

- Structure-Function Relationships in Heme Proteins. This research project is an enlarged outgrowth of previous work on hemoglobins, catalase and lactoperoxidase. The scope of the investigation includes: 1) the determination of amino acid sequence in erythrocyte catalases, 2) studies of function in relation to structure, 3) studies of human fetal hemoglobin in normal and abnormal states in order to determine the relative production of the nonallelic structural genes for the gamma chains. These data are pertinent to an evaluation of genetic status in certain abnormal hematological conditions and to the general problem of the control of protein synthesis (FY 72: $65,837).

- Pattern Recognition of Peripheral Blood Cells. The objectives of this research project are to investigate pattern recognition/procedures which will facilitate an automated classification of the cells in the peripheral blood smear. This study assumes that the morphological characteristics of the individual cells will continue to be important diagnostic criteria in hematology, and that intuitively meaningful measurements of cellular morphology (shape, size, texture, color, etc.) obtained by means of optical and digital image processing will be valuable inputs to the currently evolving automated clinical laboratories (FY 72: $23,950).

- Molecular Pathology of Genetic Disorders in Man. The objectives of this research project include: 1) the determination of the complete amino acid sequence of the human embryonic hemoglobin chain, and 2) the determination of the sequence of the beta chains of various examples of thalassemia (FY 72: $183,680).

3.8 NHLI TRAINING

The NHLI has, through its training grants and awards programs, attempted to continuously attract a sufficient number of promising young trainees, provide them with high quality training and to encourage the most capable toward academic careers to undertake advanced scientific training and supervised research.

These attempts are designed to ultimately provide optimum medical care to meet the needs of the patients with cardiovascular, pulmonary, blood and renal diseases. The Institute has attempted this through programs providing Undergraduate Training Grants, Graduate Training Grants, Fellowships, Career Development Awards, and Pulmonary Academic Awards.

A decision has been made to terminate research training programs of the NIH Institutes and Research Divisions. This will be accomplished over a phaseout period.

3.8.1 Undergraduate Training Grants

Undergraduate Training Grants were used to encourage greater emphasis on cardiovascular, cardiorenal, pulmonary and blood diseases at the undergraduate medical student level. Although worthwhile in the past, the decision was made that the primary purpose had been served, and the Institute announced discontinuance of the Undergraduate Training Grants program effective July 1972. In FY 72 the Institute supported no undergraduate training grants in Blood Diseases.

3.8.2 Graduate Research Training Programs

The Graduate Training Programs are designed to provide support for the advanced training of physicians and scientists intending to pursue an academic career devoted to fundamental or clinical research or teaching in the general areas of cardiovascular, renal, pulmonary or blood diseases. Grants for this program have been made on a competitive basis to medical schools, universities and other research--educational organizations to assist these institutions in the provision of high quality educational and training opportunities. In FY 72, the NHLI supported 10 of these programs in the area of Blood Diseases at a total of $647,416 (see Table IV-C).

3.8.3 Fellowships

The two primary objectives of the Fellowship program have been: 1) to increase the number of trained cardiovascular pulmonary and hemotologic investigators and 2) to assure the continuing flow of skilled and imaginative research workers into the cardiovascular, pulmonary, blood and related fields. Promising scientists, selected on a national competitive basis, have received these awards enabling them to obtain advanced scientific training and supervised research experience. These awards have served to encourage the research bent of young persons who show promise of becoming competent research scientists. They have also served to provide a specialized research experience and thus developed research skills. In FY 72, the NHLI supported 29 fellowships in the area of Blood Diseases; total funding was $236,373.

3.8.4 Career Development Awards

The Career Development Awards program was designed to provide stable career opportunities for scientists with outstanding potential and competence in cardiovascular, pulmonary, renal, or blood research and teaching. This award has carried significant commitments from the Institute for long-term retention of the awardees. In FY 72, in the area of Blood Diseases, there were 26 awards with total funding of $652,750.

SECTION IV

BLOOD RESOURCES

IV. BLOOD RESOURCES

Sections 4.1 through 4.6 outline NHLI supported activities correlated with the six (6) major problem areas related to the blood resource system and transplantation activities identified by the Blood Resources Panel and its task groups. The six problem areas are:

- Blood Collection (4.1)
- Fractionation and Preservation (4.2)
- Laboratory Procedures and Controls (4.3)
- Utilization (4.4)
- Systems Management (4.5)
- Transplantation (4.6).

Following this discussion is a statement on training grants and awards in the area of Blood Resources (4.7).

4.1 BLOOD COLLECTION

4.1.1 Toxicology of Plastic Devices Having Contact with Blood

The Blood Resources Branch funds and administers a contract supported program which investigates the toxicity of plastics used in the storage, transport and/or processing of blood. Both animal and human studies are included in this investigation. The animal studies have as their objective the determination of the existence and extent of toxicity to the formed elements of the blood, the lymphoreticular system, the kidney and other vital organs resulting from chronic exposure of plastics and/or their derivatives. The objectives of the human studies are: 1) to determine the prevalence, degree of exposure, and means of excretion and/or accumulation of plastic components in patients; and, 2) to determine the toxic effects, if any, of patient exposure to plastics. In FY 72, three contracts, totalling $321,340, were funded.

4.2 FRACTIONATION AND PRESERVATION

4.2.1 Standardization of Cryoprecipitate

The Blood Resources Branch funds and administers a contract supported investigation to define a standard process for producing cryoprecipitated Factor VIII which would ensure the highest yield per unit of blood. A number of variables that affect cryoprecipitate yield have and are being studied in this investigation, such as: time of storage from phlebotomy to processing, cryoprecipitate thawing time, volume of solvent, plastic composition of blood bag, type of anticoagulent used, post-exercise state of the donor, degree of mixing of freshly drawn blood, and harvesting of platelets. In FY 72, contracts, totalling $211,747, were funded.

4.2.2 Platelet Preservation

This is a contract supported program funded and administered by the Blood Resources Branch. Recognizing that the preservation of platelets for transfusion to thrombocytopenic patients is limited by platelet fragility and short life span, this program supports studies to develop techniques to increase the *in vivo* lifespan of platelets (via chemical additives, freezing techniques, etc.). In FY 72 this program supported four contracts totalling $233,330.

4.2.3 Studies on Oxygen Transport by Stored Blood

When blood is stored prior to transfusion, red blood cell 2,3 diphosphoglycerate levels decrease with a resulting shift of the hemoglobin-oxygen dissociation curve, such that oxygen is less available to the tissues. Hence, stored blood may be a less efficient transporter of oxygen than fresh blood. The Blood Resources Branch funds and administers a contract supported program to evaluate the significance of this physicochemical change upon the recipient's ability to recover from a stressful situation which requires blood transfusion. The projects are designed to study the physiologic effects of the transfusion of 2,3 diphosphoglycerate-poor blood in animals and man. In addition, means are being sought to prevent the loss of 2,3 diphosphoglycerate from stored blood. In FY 72, five contracts, totalling $225,404, were supported.

4.3 LABORATORY PROCEDURES AND CONTROLS

4.3.1 Detection of Hepatitis in Blood

This is a contract supported program funded and administered by the Blood Resources Branch in an effort to develop a rapid, sensitive method to detect HB Ag (Hepatitis B antigen), suitable for testing in blood banks.

The program consists of 10 studies which have concentrated on two different serological tests which offer the best opportunity to greatly increase assay sensitivity (i.e., the hemagglutination inhibition technique and the radioimmunoassay technique). Current efforts place emphasis on the refinement of a rapid-labelled antibody, solid phase radioimmunoassay procedure, maintaining a high level of sensitivity and specificity, as well as being HB Ag subtype specific. In FY 72, eight contracts, totalling $702,714, were funded.

4.3.2 Production and Distribution of Antibody to the Hepatitis-Associated Antigen (HB Ab) in Large Animals

The Blood Resources Branch funds and administers a contract supported effort to produce high quality HB Ab (Hepatitis B antibody) for research and educational purposes as well as to supply this reagent in areas where it is or has not been commercially available for routine blood donor testing. In FY 72, five contracts were supported. Funding is divided: approximately $42,905 was awarded for one contract totally devoted to this effort; funding of the other four contracts

comes from funds allocated to the project "Detection of Hepatitis in Blood."

4.3.3 Removal/Inactivation of the Agent of Hepatitis From Blood and Blood Products

Because testing for HB Ag (Hepatitis B antigen) does not eliminate all units of blood infections for the agent causative of hepatitis, the Blood Resources Branch funds and administers a contract supported program to develop techniques to remove or inactivate that agent. This program includes:

- A double-blind controlled clinical trial to test the efficacy of washed red cells in reducing the incidence of post-transfusion hepatitis.
- A study of various formulations of polyelectrolytes for their ability to selectively remove HB Ag from blood.
- A study of polyethylene glycol to fractionate blood into hepatitis-free components.
- Development of automated equipment to produce hepatitis-free fibrinogen.

In FY 72 the Blood Resources Branch supported three contracts in this area, totalling $133,491.

4.3.4 Epidemiology and Bioimmunology of HB Ag Carriers

While the use of blood from HB Ag carriers is known to be highly correlated with post-transfusion hepatitis, the frequency of non-parenteral spread, as well as the associated

morbidity of such individuals is unknown. The central questions addressed by this contract supported study are:

- What in the past history or present environmental circumstances differentiates the HB Ag carrier from noncarrier individuals?
- What are the routes of transmission of HB Ag, other than by blood transfusion, from the carrier to his associates, and what is the frequency of each route?
- What is the morbidity, if any, of the HB Ag carrier state as well as that of the associate to whom HB Ag is transferred by means other than transfusion?

In FY 72, four contracts, totalling $518,745, were supported.

4.3.5 Epidemiology and Development of Detection Systems for Cytomegalovirus as Transmitted by Blood Transfusion

The Blood Resources Branch funds and administers a contract supported program to: 1) define the role of transfusion in the production of cytomegalovirus infection among recipients of blood or blood components, and 2) to determine the magnitude and extent of this disease in high-risk populations. (Note: Data at present is inconclusive as to whether CMV infection results from transmission by transfused blood, or by activation of latent virus in the recipient, secondary to stimulation by foreign white cells, drugs, the stress of surgery, or other causes. Further, presently available detection systems may not be adequate for definitively resolving this problem.) In FY 72, six contracts, totalling $429,700 were supported.

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4.4 UTILIZATION

4.4.1 Donor-Recipient Identification in Blood Transfusion

The Blood Resources Branch funds and administers a contract supported program of studies (FY 72: three contracts, totalling $416,600) designed to develop systems not requiring human judgment and accuracy, and capable of performing almost all labelling and patient identification procedures from donor to recipient.

These studies resulted from the fact that each year--despite the careful screening, testing, and management of blood under carefully written standards from the time of donation--morbidity and mortality occur from transfusion reactions, due to human error.

4.4.2 Clinical Trials of Hyperimmune Gamma Globulin for Prophylaxis and Treatment of Acute Hepatitis B

This is a contract supported, controlled, double-blind, clinical trial, funded and administered by the Blood Resources Branch, designed to determine the efficacy of gamma globulin containing a high titer of hepatitis B antibody (HB Ab) in the following populations:

- Hospital personnel who were accidentally exposed to HB Ag-positive material.
- Renal dialysis patients and staff in particularly hepatitis-prone centers.
- Patients with acute fulminant hepatitis.
- Cardiovascular surgery patients receiving large-volume transfusions.

In FY 72, four contracts, totalling $964,213 were funded.

4.4.3 The Removal of Histocompatibility Antigens from Blood

This is a contract supported program of research funded and administered by the Blood Resources Branch (FY 72: four contracts, totalling $180,830), aimed at evaluating processes for removing white cells from the blood. The research is undertaken recognizing that patients who receive transplanted organs often require blood transfusions prior to the transplantation. When the patients are transfused they may become sensitized to the white cell and platelet histocompatibility antigens present in whole blood. If such occurs, the incidence of rejection of the transplanted organ is much higher than if the patient has not received the blood transfusion(s). Since many of these patients are anemic and must be transfused, it is desirable to remove as many white cells and platelets as possible from the blood before transfusion--thus reducing the incidence of sensitization and early rejection.

4.4.4 Automated Donor Blood Inventory--Donor Blood Recipient Information System

The Blood Resources Branch in its Blood Procurement and Distribution Systems Program funds and administers a contract supported investigation of the efficacy of computers in promoting safety, proper distribution, and reduced waste of our national blood resource. It has been determined that possible computer services include: donor recruiting, donor group records and group control, blood inventory and forecasting, blood distribution, performance statistics and accounting. (Note: savings from the use of computers arise principally

from achievement of more effective management of blood collection and inventories, not from reduction in clerical costs.) In FY 72, three contracts, totalling $319,782, were supported.

4.5 SYSTEMS MANAGEMENT

4.5.1 Operations Research Study of the American Blood System

The Blood Resources Branch, in its Blood Procurement and Distribution System program, funds and administers this contract supported systematic study of blood banking in America.* This study has three major parts:

- An overall description of the existing blood system (including the role played by the pharmaceutical industry, and major organizations such as the American Red Cross and the American Association of Blood Banks; regulatory arrangements; and an in-depth study of the functioning of a sample of blood banks).
- A study of the problem of hemophilia care as an example of the interaction of the problems facing the blood banking system.
- A study of government regulation of the Nation's blood resource, conducted to identify and assess current regulation at the Federal and State levels.

* This contract was supported, in fiscal year 1972, for $37,100 (from FY 72 funds plus carry over from the FY 71 funding of $302,000).

4.6 TRANSPLANTATION

The Division of Blood Diseases and Resources funds and administers grant supported studies in the area of transplantation (FY 72: 30 grants, totalling $1,705,964). These studies include investigations related to the use and effect(s) of immunosuppressive agents, refinement of tissue typing and related procedures for determining donor-recipient compatibility in order to achieve the best possible match and thus minimize rejection problems.

4.7 NHLI TRAINING

The NHLI has, through its training grants and award programs, attempted to continuously attract a sufficient number of promising young trainees, provide them with high quality training and to encourage the most capable toward academic careers to undertake advanced scientific training and supervised research. These attempts are designed to ultimately provide optimum medical care to meet the needs of the patients with cardiovascular, pulmonary, blood and renal diseases. The Institute has attempted this through programs providing Undergraduate Training Grants, Graduate Training Grants, Fellowships, Career Development Awards and Pulmonary Academic Awards. (Note: A decision has been made to terminate research training programs of the NIH Institutes and Research Divisions. This will be accomplished over a phase-out period.)

4.7.1 Undergraduate Training Grants

Undergraduate Training Grants were used to encourage greater emphasis on cardiovascular, cardiorenal, cardiopulmonary and blood diseases at the undergraduate medical student level. Although worthwhile in the past, the decision was made that the primary purpose had been served, and the Institute announced discontinuance of the Undergraduate Training Grants program effective July 1972. In FY 72 the NHLI supported no Undergraduate Training Grants in Blood Resources.

4.7.2. Graduate Research Training Programs

The Graduate Training Programs are designed to provide support for the advanced training of physicians and scientists intending to pursue an academic career devoted to fundamental or clinical research or teaching in the general area of cardiovascular, renal, pulmonary or blood diseases. Grants for this program have been made on a competitive basis to medical schools, universities and other research--educational organizations to assist these institutions in the provision of high quality educational and training opportunities. In FY 72, the NHLI supported one program in Blood Resources, total funding was $53,112.

4.7.3 Fellowships

The two primary objectives of the Fellowship program have been: 1) to increase the number of trained cardiovascular and pulmonary investigators and 2) to assure the continuing flow of skilled and imaginative research workers into the cardiovascular, pulmonary, blood and related fields. Promising scientists, selected on a national competitive basis, have received these awards enabling them to obtain advanced scientific training and supervised research experience. These awards have served to encourage the research bent of young persons who show promise of becoming competent research scientists. They have also served to provide specialized research experience and thus developed their research skills. In FY 72, the NHLI supported one fellowship in the area of Blood Resources; total funding was $8,500.

4.7.4 Career Development Awards

The Career Development Awards program was designed to provide stable career opportunities for scientists with outstanding potential and competence in cardiovascular, pulmonary, renal or blood research and teaching. This award has carried significant commitments from the Institute for long-term retention of the awardees. In FY 72, no awards in Blood Resources were made.

APPENDIX

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APPENDIX

SUMMARY OF NATIONAL HEART AND LUNG INSTITUTE RESEARCH GRANT AND CONTRACT SUPPORT FOR FISCAL YEAR 1972

Presented in the following tables are extramural program cost data prepared February 8, 1973, by the Reports and Evaluation Branch, Division of Extramural Affairs, National Heart and Lung Institute.* All textual references to tables relate to the tables presented in this appendix.

The data presented herein is undergoing further review and analysis as a part of continuing NHLI planning and evaluation activities.

* In this context, "extramural" is defined as all NHLI programs exclusive of the Institute's Intramural Program.

RESEARCH GRANTS AND CONTRACTS DISPLAYED BY
PANEL AND TASK GROUP CATEGORIES
(Tables I-A through I-E)

TABLE I-A

FY 72 Research Grants and Contracts Displayed by
Heart and Blood Vessel Diseases Panel
February 8, 1973

Task Group	Grants		Contracts	
	Number	Funds	Number	Funds
Atherosclerosis	159*	$16,498,303	23	$ 6,231,075
Coronary Heart Diseases	127	10,204,086	97	21,223,534
Peripheral Vascular Diseases	31	1,503,266	-	-
Stroke	13	464,068	-	-
Hypertension	214	14,322,753	9	3,970,833
Congenital Heart Disease	28	1,870,262	-****	-
Rheumatic Fever/Rheumatic Heart Diseases	15	890,571	-****	-
Cardiomyopathy	4	149,503	-	-
Arrhythmia	66	2,637,911	(7)	(379,970)***
Cardiac Failure	68	2,868,742	16	942,248
Shock	50	2,473,872	-	-
Other				
Artificial Heart**	27	3,742,252	-	-
Cardiac Diseases	44	4,038,829	-	-
Cardiovascular Dynamics	178	9,340,639	-	-
Multicategorical Cardiac Diseases	29	16,692,362	-	-
Basic Research	28	1,308,780	-	-
Total	1081	$89,006,199	145	$32,367,690

* Includes Arteriosclerosis

** Includes 4 grants concerned chiefly with Thromboembolism in Relation to Prosthetic Devices

*** Included in contract totals for Coronary Heart Diseases

**** Selected contracts from the Divisi ı of Technical Applications (in Biomaterials and Bioinstrumentation) could be tabulated here

TABLE I-B

FY 72 Research Grants and Contracts Displayed by Lung Diseases Panel
February 8, 1973

Task Group	Grants** Number	Grants** Funds	Contracts Number	Contracts Funds
Bronchiolitis and Childhood Obstructive Diseases	3	$ 140,018	-	$ -
Cystic Fibrosis and Other Genetic Lung Diseases	4	101,144	7*	368,685
Extrapulmonary Effects of Respiratory Diseases	6	236,895	-	-
Consolidated Task Group for:				
a. Environmental Respiratory Diseases	29	1,786,353	-	-
b. Infectious Respiratory Diseases	1	41,740	-	-
c. Emphysema & Chronic Bronchitis	119	5,457,678	8	879,970
d. Sarcoid Lung Diseases	6	288,030	-	-
e. Diffuse Interstitial Respiratory Disease	6	424,751	-	-
f. Acute & Chronic Respiratory Failure	55	2,362,934	13	826,254
g. Hypersensitivity Lung Diseases	6	1,028,955	-	-
h. Cor Pulmonale	7	135,785	-	-
i. Pulmonary Hypertension	17	649,336	-	-
j. Pulmonary Edema	15	562,520	-	-
k. Hyaline Membrane Disease of the Newborn	11	1,444,648	-	-
l. Normal Lung	22	710,685	-	-
m. Allergic Airway Disease--Asthma	7	340,602	-	-
n. Education	103	4,457,395	-	-
Total	417	$20,169,469	28	$2,074,909

* Includes Alpha-1-Antitrypsin studies.

** The number and funds for grants are based on an analysis by the Division of Lung Diseases.

The number of grants reflects the number of sub-projects concerned with these disease areas and not the actual number of grants.

TABLE I-C

FY 72 Research Grants and Contracts Displayed by Blood Diseases Panel
February 8, 1973

Task Group	Grants		Contracts	
	Number	Funds	Number	Funds
Hemophilia and Other Bleeding Disorders	11	823,994	-	$ -
Arterial Thromboembolism	36	2,445,684	1	66,480
Hemorrhagic Disorders Due to Platelet Abnormalities	13	546,689	-	-
Venous Thrombosis and Pulmonary Embolism	24	993,882	8	670,666
Thromboembolism in Relation to Prosthetic Devices	(4)*	(147,353)	-	-
Microcirculatory Thrombosis	3	418,344	-	-
Hemoglobinopathies	113	9,498,960	39	4,493,255
Basic Clotting Studies	53	3,492,746	-	-
Other	24	963,132	-	-
Total	277	$19,183,431	48	$5,230,401
	(4)	(147,353)		

*Also included in Division of Heart and Vasular Diseases under Artificial Heart

TABLE I-D

FY 72 Research Grants and Contracts Displayed by Blood Resources Panel
February 8, 1973

Task Group	Grants		Contracts	
	Number	Funds	Number	Funds
Blood Collection	-	$ -	3	$ 321,340
Processing I (Fractionation and Preservation)	9	461,628	13	688,105
Processing II (Laboratory Procedures and Controls)	11	1,929,610	23	1,966,273
Utilization	1	32,700	11	1,561,643
Distribution and Systems Management	-	-	1	37,100
Transplantation	30	1,705,964	-	-
Total	51	$4,129,902	51	$4,574,461

TABLE I-E

FY 72 Research Grants and Contracts in Miscellaneous Category
February 8, 1973

Task Group	Grants Number	Grants Funds	Contracts Number	Contracts Funds
Miscellaneous	-	-	11	$337,084

Explanation of Miscellaneous Category

The following contracts and reimbursable agreements were not administered by the program branches:

Number	Funding Account	Title	Funds
R72-0006	Labs & Clinics	Instrument Shop Work on Calorimeter Mixers	$ 1,000
R72-0008	Labs & Clinics	Metabolic Changes in Separation of Particular Cells	20,000
C69-2246	Labs & Clinics	Neural Coding of Brain Cells	49,850
C71-2008	Labs & Clinics	In Vitro Studies of Neurological Tissues	69,457
C72-2904	Labs & Clinics	Collection of Medical and Lipid Data	5,000
C72-2055	Labs & Clinics	Development & Evaluation of Blood Oxygenators	68,284
C70-2216	Labs & Clinics	Develop Biological Flow NMR Concepts	59,500
R72-0009	Review & Approval	Autopsy Records Demographic Data--3 Classes of Death	4,500
C69-0095	Office of the Director	Transplantation Registry	46,493
C71-2327	Office of the Director	Contribution of Basic Science to Heart and Lung	7,000
C72-3852	Collaborative General	XII Intl Congress on Internal Medicine	6,000
Total			$337,084

GRAND TOTAL	Contracts	283	$ 44,584,545
	Grants	1,826	132,489,001

AVERAGE COST OF GRANTS AND CONTRACTS
(Tables II-A and II-B)

TABLE II-A

FY 72 Average Cost Per Research Contract
Within Each Funding Branch
February 8, 1973

Funding Branch	Average Cost
Clinical Applications (Excluding Multi-Risk Factor Intervention Trial and Hypertension Detection and Follow-Up Program)	$ 88,647
Biometry and Epidemiology	82,269
Respiratory Diseases	75,476
Medical Devices Applications Program (Excluding Test and Evaluation Centers)	114,491
Myocardial Infarction Branch (Excluding MIRU's)	83,202
National Blood Resource Program (Excluding UPET and Sickle Cell Trials)	80,832
Miscellaneous (Intramural, Review and Approval, Office of the Director, Collaborative General)	30,644
Average for funding branches as shown above	$ 87,180
Average for Clinical Trials and Special Programs (The following items are included in this category: Lipid Metabolism Centers and Labs; Hypertension Detection and Follow-Up; Multi-Risk Factor Intervention Trial; MDAP's T&E Centers; MIRU's; UPET; Sickle Cell Clinical Trial; Sickle Cell Reimbursable Agreement with HSMHA; Drug Study Coordinating Center)	$436,523

TABLE II-A (Worksheet)

FY 72 Average Cost of Research Contracts
January 17, 1973

	No.		Funds		Average
Labs and Clinics	7		$ 273,091		$ 39,013
Review and Approval	1		4,500		4,500
Office of the Director	2		53,493		26,747
Collaborative General	1		6,000		6,000
Drug Study	1		423,700		423,700
Clinical Applications	24		7,771,153		
- HT		9		3,970,833	
- MRFIT		9		3,268,440	
	-18		-7,239,273		
	6		531,880		88,647
Biometry and Epid.	7		575,886		82,269
Lipid Metabolism	13		5,475,000		
Respiratory Diseases	21		1,585,000		75,476
MDAP	60		10,584,519		
- T&E Centers	-2		-3,944,018		
	58		6,640,501		114,491
Myocardial Infarction	47		8,027,341		
- MIRU	-9		-4,865,668		
	38		3,161,673		83,202
NBRP	98		7,829,862		
- UPET		6		296,303	
- SC Trial		7		662,840	
	-13		-959,143		
	85		6,870,719		80,832
Sickle Cell	1		1,975,000		1,975,000

TABLE II-B

FY 72 Average Cost Per Research Grant Within Each Funding Branch*
February 9, 1973

FUNDING BRANCH	AVERAGE COST			
	Research Grants	Program Projects	SCOR	Sickle Cell Centers
Arteriosclerosis	$ 55,237	$ 336,177	$ 634,304	$ -
Cardiac Diseases	42,023	294,065	-	-
Hypertension and Kidney Diseases	45,427	367,213	499,160	-
Pulmonary Diseases	43,554	295,647	380,421	-
Thrombosis and Hemorrhagic Diseases	44,858	420,417	421,290	-
Special Programs	48,928	605,105	-	-
Therapeutic Evaluations	57,322	-	-	-
Sickle Cell	31,776	-	-	480,383

*Based on Total Obligations

DOLLAR DISTRIBUTION BY BUDGET CATEGORIES
FOR GRANTS AND CONTRACTS
(Tables III-A through III-D)

NHLI

TABLE III-A

FY 72 Research Grants* Dollar Distribution by Budget Category
According to National Plan Panels
February 9, 1973

	Heart	Lung	Blood Diseases	Blood Resources***
Sample Size:				
1. Number	226	139	131	20
2. Percent	21%	76**	47%	39%
Budget Category Average $/Project@				
1. Personnel	$26,313	$23,461	$28,509	$31,861
2. Consultants	163	204	30	103
3. Equipment	2,216	2,601	1,900	1,259
4. Supplies	6,518	5,804	4,903	4,214
5. Domestic Travel	605	608	641	821
6. Foreign Travel	10	29	33	-
7. Hospitalization	105	65	51	-
8. Outpatient Costs	35	23	41	25
9. Alterations	13	14	2	-
10. Publications	411	364	459	1,016
11. Other	2,218	1,810	1,413	1,362
12. Total Direct Costs	38,606	34,982	37,976	40,660

* Includes regular research grants only. Excludes Program Projects, SCORS, and Sickle Cell Centers

** Based on number of grants officially reported for FY 1972

*** Excludes transplantation. Includes all regular research grants classified as Fractionation and Preservation, Laboratory Procedures and Controls, and Utilization

@ Includes unexpended balance from previous year

TABLE III-B

FY 72 Research Contracts Dollar Distribution by Budget Category
According to National Plan Panels
February 2, 1973

	Heart	Lung	Blood Diseases	Blood Resources
Sample Size:				
1. Number	41	8	16	15
2. Percent	38%	38%	38%	35%
Budget Category				
Average $/Project:				
1. Personnel	$ 45,995	$46,611	$28,231	$ 61,596
2. Consultants	3,892	662	88	52
3. Equipment	2,573	9,150	4,756	6,217
4. Supplies	15,409	8,659	5,256	8,293
5. Travel	1,656	1,077	353	2,740
6. Patient Costs	385	750	1,725	2,392
7. Alterations	-	112	-	-
8. Publications	-	-	-	-
9. Fees	3,590	-	394	-
10. Other	16,366	5,326	5,787	23,949
11. Overhead	37,528	14,935	14,768	23,458
12. Total Project	127,395	87,283	61,357	128,696
13. Unexpended Balance	1,958	611	1,580	744
14. Obligation	125,437	86,672	59,777	127,923

Note: Special programs and clinical trials are not included in these calculations

TABLE III-C

FY 72 Research Contracts Dollar Distribution by Budget Category
According to Former Program Branches That Now Fall in
Heart and Vascular Diseases Division
February 2, 1973

	MI	MDAP	CA	All HV
Sample Size:				
1. Number	15	20	6	
2. Percent	39%	34%	46%	
Average $/Project:				
1. Personnel	$39,562	$ 49,479	$50,464	$ 45,995
2. Consultants	2,698	5,445	1,700	3,892
3. Equipment	4,504	1,654	806	2,573
4. Supplies	8,759	22,918	7,001	15,409
5. Travel	1,698	885	4,125	1,656
6. Patient Costs	753	-	750	385
7. Alterations	-	-	-	-
8. Publications	-	-	-	-
9. Fees	-	7,358	-	3,590
10. Other	16,139	17,108	14,460	16,366
11. Overhead	19,483	58,041	14,267	37,528
12. Total Project	93,598	162,889	93,574	127,395
13. Unexpended Balance	3,207	345	4,209	1,958
14. Obligation	90,391	162,544	89,365	125,437

Note: Special programs and clinical trials are not included in these calculations.

TABLE III-D

FY 72 Research Contracts Summary of Samples Chosen for Budget Category Analysis
February 2, 1973

Branch	No. of Contracts Paid FY 72	No. of Special Contracts	Balance	30% of Balance	Actual No. in Sample	% of Sample
LM	13	13 (LR clinics)	0	0	0	-
RD	21	-	21	6	8	38%
MDAP	60	2 (T&E)	58	17	20	34%
MI	47	9 (MIRU's)	38	11	15	39%
NBRP	Res. 43	-	43	13	15	35%
	Div. 55	13 (UPET-6 SC-7)	42	13	16	38%
CA (Includes B&E and Drug Study)	32	19 (MRFIT-9 HYT-9 DRUG-1)	13	4	6	46%
SC	(RA) 1	1	0	0	0	-
Other (Intramural, R&A, OD, CG)	11	-	11	3	0	-
Total	283	57	226	67	80	35%

TRAINING AND FELLOWSHIPS
(Tables IV-A through IV-C)

TABLE IV-A

FY 72 Distribution of Graduate Research Training Grants
According to National Plan Panels
January 12, 1973

Program	No. of Training Grants	Total Funds Awarded	Average $ Per Grant	Trainees Recommended				Trainees Assigned*			
				Full-Time		Part-Time		Full-Time		Part-Time	
				Pre	Post	Pre	Post	Pre	Post	Pre	Post
Heart and Blood Vessel Diseases	197	$12,335,331	$62,615	189	677	187	14	138	494	172	96
Lung Diseases	40	2,813,025	70,325	22	182	17	-	16	128	8	10
Blood Diseases	10	647,416	64,741	17	31	6	-	12	23	1	3
Blood Resources	1	53,112	53,112	-	2	-	-	-	2	-	-
Total	248	$15,848,884	-	228	892	210	14	166	647	181	109

*Based on receipt of (2271) Statement of Appointment of Trainee.

TABLE IV-B

FY 72 Distribution of Fellowship Funds
January 16, 1973

Program	Fellowships with Stipends: No.	Average Stipend	Total Stipends	Tuition Dependency & Supply Allow.	Total: Fellows	Paid
POSTDOCTORAL FELLOWSHIPS						
Heart & Blood Vessel Diseases	53	$ 7,132	$378,003	$45,722	76	$423,725
Lung Diseases	7	7,642	53,500	4,000	8	57,500
Blood Diseases	18	6,046	108,833	17,391	26	126,224
Blood Resources	1	8,500	8,500	1,000	1	9,500
TOTAL	79	$ 6,947	$548,836	$68,113	111	$616,949
SPECIAL FELLOWSHIPS						
Heart & Blood Vessel Diseases	43	$10,552	$453,760	$59,646	81	$513,406
Lung Diseases	11	10,240	112,640	16,912	25	129,552
Blood Diseases	11	11,640	128,040	10,765	21	138,805
Blood Resources	-	-	-	-	-	-
TOTAL	65	$10,683	$694,440	$87,323	127	$781,763

TABLE IV-C

FY 72 Distribution of Training Funds in Four Programs
January 16, 1973

Type of Training	Heart & Blood Vessel Diseases			Lung Diseases			Blood Diseases			Blood Resources			Training Total		
	No.	Funds	Avg. Funds	No.	Funds	Avg. Funds	No.	Funds	Avg. Funds	No.	Funds	Avg. Funds	No.	Funds	Avg. Funds
Undergraduate Training Awards	114	$ 2,705,648	$23,733	-	$ -	$ -	-	$ -	$ -	-	$ -	$ -	114	$ 2,705,648	$23,733
Graduate Research Training Grants	197	12,335,331	62,615	40	2,813,025	70,325	10	647,416	64,741	1	53,112	53,112	248	15,848,884	63,906
Pulmonary Academic Awards	-	-	-	16	727,790	45,486	-	-	-	-	-	-	16	727,790	45,486
Postdoctoral Fellowships*	53	378,003	7,132	7	53,500	7,642	18	108,833	6,046	1	8,500	8,500	79	548,836	6,947
Special Fellowships*	43	453,760	10,552	11	112,640	10,240	11	128,040	11,640	-	-	-	65	694,440	10,683
Career Development Awards (K3)	41	1,207,203	29,443	8	221,132	27,641	7	194,448	27,778	-	-	-	56	1,622,783	28,978
Career Development Awards (K4)	51	11,190,784	23,348	13	287,910	22,146	17	395,635	23,272	-	-	-	81	1,874,329	23,139
Career Awards	17	511,208	30,071	8	241,398	30,174	2	62,667	31,333	-	-	-	27	815,273	30,195
Program Total	516	$18,781,937		103	$4,457,395		65	$1,537,039		2	$61,612		686	$24,837,983	

*Numbers and funds reflect fellows who were paid stipends.
Tuition, dependency and/or supply allowance is not included.
For total fellowship funds see Distribution of Fellowship Funds.

SPECIALIZED CENTERS OF RESEARCH
(Table V)

TABLE V

FY 72 Specialized Centers of Research
January 11, 1973

	No.	Funds	Average $ Per Award
Arteriosclerosis	15	$ 9,514,566	$634,304
Hypertension	5	2,495,798	499,160
Pulmonary Disease	17	6,467,151	380,421
Thrombosis	5	2,106,448	421,290
Total	42	$20,583,963	
Average award for SCOR Program			$490,094

SPECIAL PROGRAMS, GRANTS AND CONTRACTS,
BUDGET AND PERSONNEL COST ANALYSIS
(Tables VI-A through VI-C)

TABLE VI-A

FY 72 Research Grants and Contracts Personnel Cost Analysis for Special Programs
February 2, 1973

Program	Number of Projects	Total Funds	Total Personnel Costs	Average Manpower/Project: Professional Salaried No.	Professional Salaried Eq.+	Professional Non Salaried No.	Professional Non Salaried Eq.+	Professional Non Salaried Cost	Non-Professional Salaried No.	Non-Professional Salaried Eq.+	Non-Professional Salaried Cost	Average Personnel Cost	Average Cost Per Project	Cost of Entire Trial[1,2]
Sickle Cell Centers	10	$ 4,803,828[3]	$ 2,711,971	7.3	3.4	8.8	1.4	$ 80,935	23.8	18.9	$190,262	$271,197	$480,383	
Program Projects	74	34,382,142[3]	18,756,008	10.3	6.2	7.8	2.1	112,598	18.8	15.3	140,982	253,459	464,624	
Lipid Clinics	11	5,120,049[1,4]	2,498,956	10.7	5.3	7.1	1.7	-	22.9	15.6	-	227,178	466,524	5,710,659
Central Patient Registry	1	495,610	264,557	8.0	4.0	-	-	-	18.0	16.2	-	-	-	-
Lipid Standardization Lab	1(R.A.)	95,000	*	*	*	*	*	-	*	*	-	-	-	-
MIRU's	9	6,510,905[1]	3,325,274	14.7	6.9	6.2	1.2	-	23.7	19.9	-	369,475	723,434	6,510,905

* Data not available.
1. Represents cost before unexpended balance is subtracted, (allocated funds).
2. Laboratories, patient registries, coordinating centers, etc., are included in these calculations. They are not included in the other statistics shown.
3. Represents actual award for FY 1972.
4. Plus 11,710 for foreign currency exchange.
\+ Number of full-time equivalents.

TABLE VI-B

FY 72 Research Grants Budget Analysis for Special Programs
February 6, 1973

	Program Projects	Sickle Cell Centers	SCOR's
Number of Grants	74	10	42
Average $ per Grant:*			
1. Personnel	$ 254,096	$ 247,823	$241,003
2. Consultants	2,084	4,740	1,749
3. Equipment	24,007	25,185	26,386
4. Supplies	42,247	22,475	48,379
5. Domestic Travel	4,947	5,290	6,488
6. Foreign Travel	16	-	50
7. Hospitalization	16,351	35,516	14,109
8. Outpatient Costs	1,667	-	2,056
9. Alterations	1,106	10,680	6,413
10. Publications	2,398	1,951	959
11. Other	25,446	46,458	65,683
12. Indirect Costs	108,672	79,364	107,810
13. Total	483,124	480,383	521,340
14. Unexpended Balance	18,501	0	31,246
15. Obligation	464,624	480,383	490,094

*Average calculated on total cost of grant, not obligated funds.

TABLE VI-C

FY 72 Research Contracts Budget Analysis for Selected Programs
January 31, 1973

	Lipid Clinics	MIRU's
Number of Contracts	11	9
Average $ Per Contract:*		
Personnel	$227,178	$369,475
Consultant Services	-	-
Equipment	43,451	44,927
Supplies	36,064	68,026
Travel	10,134	5,928
Hospitalization	9,421	9,095
Outpatient Costs	11,258	3,518
Alterations	864	-
Publications	745	2,839
Other	31,123	54,172
Overhead	95,221	161,454
Total	$466,524	$723,434

*Averages calculated on total cost of project, not obligated funds. Laboratories, patient registries, coordinating centers are not included in these calculations.

CLINICAL TRIALS, GRANTS AND CONTRACTS,
BUDGET AND PERSONNEL COST ANALYSIS
(Tables VII-A through VII-F)

TABLE VII-A

FY 72 Research Grant Personnel Cost Analysis for Clinical Trials
February 1, 1973

Program	Number of Projects	Total Funds*	Total Personnel Costs	Average Manpower/Project: Professional Salaried No.	Professional Salaried Eq.+	Professional Non Salaried No.	Professional Non Salaried Eq.+	Professional Cost	Non-Professional Salaried No.	Non-Professional Salaried Eq.+	Non-Professional Cost	Average Personnel Cost	Cost-Entire Trial**	Cost/Patient Year**
Drug Study														
Clinical Trials	55	$4,213,014	$2,585,928	3.6	1.0	0.7	0.1	$ 27,578***	2.9	2.3	$ 20,443***	$ 47,017	$5,180,425	$ 836
Coordinating Center	1	526,600	298,091	7.0	4.6	-	-	94,479***	27.0	25.5	211,254***	298,091		
Central Laboratory@	1	423,700	352,120	-	-	-	-	-	-	-	-	352,120		
Statistical Analysis@	1	17,111	-	-	-	-	-	-	-	-	-	-		
Essential Hypertension														
Clinical Trials	6	225,217	147,761	0.3	0.2	2.0	0.6	3,211***	2.5	2.0	20,840***	24,627	338,981	803
Coordinating Center	1	113,764	60,000	1.0	0.1	1.0	0.2	2,500***	7.0	4.3	62,367***	60,000		

+ Number of full time equivalents.

* Represents cost before unexpended balance is subtracted.

** Laboratories and coordinating centers are included in these calculations. They are not included in the other statistics.

*** Personnel funds requested.

@ Contract.

TABLE VII-B

FY 72 Research Contracts Personnel Cost Analysis for Clinical Trials
February 2, 1973

Clinical Trial	No. of Contracts	Total[1] Funds	Total Personnel Costs	Average Manpower/Contract: Professional Salaried No.	Professional Salaried Eq.+	Professional Non-Salaried No.	Professional Non-Salaried Eq.+	Non-Professional Salaried No.	Non-Professional Salaried Eq.+	Personnel Costs	Entire Trial[1,2]	Cost/ Patient Year[2]
Hypertension Detection and Followup	8*	$3,363,038	$1,950,964	6.5	2.7	2.0	0.2	21.0	17.8	$243,870	$4,004,833	-[3]
Coordinating Center	1	641,795	160,711	0.0	0.0	4.0	0.7	18.0	15.3			
Multi-Risk Factor Intervention Trial	8	3,068,946	1,574,100	6.5	4.1	1.6	0.3	10.0	9.0	196,762	3,268,446	-[3]
Coordinating Center	1	199,500	64,869	10.0	2.4	0.0	0.0	3.0	2.0			
Urokinase-Streptokinase Pulmonary Embolism Trial	5	265,259	105,576	1.8	0.6	2.0	0.1	4.8	1.9	26,392	351,803	1,999[3]
Coordinating Center	1	31,044	20,656	2.0	0.2	0.0	0.0	4.0	2.0			
Personal Services	8	55,500										
Sickle Cell Therapy	7	643,117	229,988	5.0	0.8	0.3	0.0	3.3	1.9	32,855	643,117	6,496[3]

[1] Represents cost before unexpended balance is subtracted.

[2] Laboratories, patient registries, and coordinating centers, (if any), are included in these calculations. They are not included in the other statistics shown.

[3] See explanatory notes below.

[4] Budget and personnel breakdowns not available for Reimbursable Agreement involved. Figures based on data from the four participating contractors funded in 1972.

[+] Number of full-time equivalents.

*14 contracts actually awarded (six were no cost time extensions).

Footnote #3, February 2, 1973, Research Contracts Summary of Samples Chosen for Budget Category Analysis.

Explanation of patient numbers, cost/patient year, and overall costs as shown.

Multirisk Factor Intervention Trial--In fiscal 72 there were no patients. Costs shown were for planning. Eight centers and one coordinating center were established. Twelve more centers may be funded in the spring, bringing the total number of centers to 20. An RFP is being issued for an ECG Center. New patients should enter the program in the spring. Eventually there should be 600 patients per center, for a total of 11-12,000 in the program. The study will run for six years plus followup. The cost of the program in its second year should be around 7 million; subsequent years will probably cost 12.1 million each.

Hypertension Detection and Followup Study--In fiscal 72 there were no patients. Cost shown were for planning and pilot studies. Costs for fiscal 73 should be around 7.2-7.4 million. Screening will begin at the end of January, with over half of the 10,000 patients accumulated by the end of the fiscal year. FY 74 costs should be around 6.8 million and costs for the subsequent five years should hover around 6.4-6.5 million. A coordinating center at Texas U. School of Public Health, a central lab at Northwestern, and a central ECG lab at the University of Minnesota are active now. The cost/patient year was estimated as $600-700 when calculating the costs for both treated patients and controls. Treated patients average cost $750-800 per year while the controls averaged around $500-550 per year.

Urokinase-Streptokinase Pulmonary Embolism Trial--There were 176 patients in Phase II of this trial. The clinical part of this trial will conclude on June 30 of this year; the personal services contract for reading of photoscans will end on September 30. There is a $600,000 procurement contract for urokinase preparation from May 1970 through February 1973.

Sickle Cell Treatment Trial--To this point there are 99 patients. Another 50 should enter the trial by June.

TABLE VII-C

FY 72 Research Grants Budget Analysis for Clinical Trials
February 5, 1973

	Drug Study	Essential Hypertension
Number of Grants	55	6
Average $ per Grant:*		
1. Personnel	$ 47,017	$ 24,626
2. Consultants	316	300
3. Equipment	163	179
4. Supplies	1,949	1,358
5. Domestic Travel	1,965	1,280
6. Foreign Travel	-	-
7. Hospitalization	1,414	-
8. Outpatient Costs	5,940	-
9. Alterations	27	-
10. Publications	-	-
11. Other	1,953	697
12. Indirect Costs	15,853	9,095
13. Total	76,600	37,536
14. Unexpended Balance	22,278	0
15. Obligation	54,322	37,536

*Averages calculated on total cost of grant, not obligated funds. Laboratories, patient registries, coordinating centers are not included in these calculations.

TABLE VII-D

FY 72 Research Contracts Budget Analysis for Clinical Trials
February 2, 1973

	Hypertension	MRFIT	Sickle Cell	UPET
Number of Contracts	8	8	7	5
Average $ per Contract:*				
1. Personnel	$ 243,870	$ 196,762	$ 32,855	$ 26,392
2. Consultants	1,388	1,765	393	-
3. Equipment	10,584	27,547	-	5,293
4. Supplies	14,988	23,423	5,666	1,798
5. Travel	3,426	6,789	1,721	500
6. Hospitalization	7,438	1,382	8,735	13,010
7. Outpatient costs	17,481	250	-	-
8. Alterations	10,611	2,812	-	-
9. Publications	425	-	-	-
10. Other	50,128	51,956	24,773	1,450
11. Indirect/OH	70,090	70,930	17,729	9,533
12. Total	430,928	383,618	91,874	57,975
13. Unexpended balance	10,549	1	-	1,994
14. Obligation	420,380	383,617	91,874	55,981

*Averages calculated on total cost of project, not obligated funds. Laboratories, patient registries, coordinating centers are not included in these calculations.

TABLE VII-E

FY 72 Research Contracts, Clinical Applications and Prevention, DHVD
August 18, 1972

Contractor	Number	Prior Funds	FY 72 Period	FY 72 Funds	MOD #	Principal Investigator
Pittsburgh University Pittsburgh, Pa.	C71-2006	$ 15,628	7- 0-71 to 6- 0-72	$ 17,111 17,111**	(MO3)	Cornfield, Jerome
Center for Disease Control Atlanta, Ga.	R65-0002	2,539,500	7-01-71 to 6-30-72	423,700 423,700**	(M58)	Mather, Alan
*Boston City Hospital Boston, Mass.	C71-2433	229,300	0- 0- 0 to 0- 0- 0 6-28-72 to 6-27-73	000 560,000 560,000**	(MO1) (MO2)	Kass, Edward H.
*Evans County Health Department Claxton, Ga.	C71-2434	126,576	6-30-72 to 8-29-72	000 000**	(MO1)	Hames, C. G.
*Utah U College of Medicine Salt Lake City, Utah	C71-2435	148,625	6- 0-72 to 4-21-73	429,150 429,150**	(MO1)	Reamer, Virginia L.
*Cedars-Simai Medical Center Los Angeles, Cal.	C71-2436	303,600	6-24-72 to 8-31-72	000 000**	(MO2)	Maxwell, Morton
*Mississippi U Sch of Medicine Jackson, Miss.	C71-2437	199,680	0- 0- 0 to 0- 0- 0 6-28-72 to 9-30-72	000 000 000**	(MO1) (MO2)	Langford, Herbert G.
*Georgetown University Washington, D.C.	C71-2438	215,600	0- 0- 0 to 0- 0- 0 5-21-72 to 7-20-72	000 000 000**	(MO1) (MO2)	Finnerty, Frank Jr.
*Maryland U School of Medicine Baltimore, Md.	C71-2439	278,000	0- 0- 0 to 0- 0- 0 0- 0- 0 to 0- 0- 0 6-30-71 to 8-31-72	000 000 000 000**	(MO1) (MO2) (MO3)	Henderson, Maureen
*Alabama University Birmingham, Ala.	C71-2440	243,450	0- 0- 0 to 0- 0- 0 0- 0- 0 to 0- 0- 0 6-30-72 to 6-29-73	$ 000 000 476,365 476,365**	(MO1) (MO2) (MO3)	Schnaper, Harold
*Northwestern University Evanston, Ill.	C71-2441	324,600	0- 0- 0 to 0- 0- 0 0- 0- 0 to 0- 0- 0 6-14-72 to 8-31-72	000 000 000 000**	(MO1) (MO2) (MO3)	Stamler, Jeremiah
*Texas U Sch of Public Health Houston, Tex.	C71-2442	122,863	6-28-72 to 6-27-73	607,795 607,795**	(MO1)	Remington, Richard D.
*Albert Einstein College of Med New York, N.Y.	C72-2931	000	6-28-72 to 6-27-73	403,312 403,312**	(MOO)	Blaufox, M. Donald
*Mount Sinai Hosp Minneapolis Minneapolis, Minn.	C72-2937	000	6-30-72 to 6-29-73	382,993 382,993**	(MOO)	Berman, Reuben

*Hypertension Detection and Followup Study
**Total Contract Funding - FY 72

TABLE VII-E (Continued)

Contractor	Number	Prior Funds	FY 72 Period	FY 72 Funds	MOD #	Principal Investigator
*Emory University Atlanta, Ga.	C72-2938	000	6-25-72 to 6-24-73	383,382 383,382**	(M00)	Gilbert, Charles A.
*Michigan State University East Lansing, Mich.	C72-2939	000	6-30-72 to 6-29-73	328,836 328,836**	(M00)	Daugherty, S.
*California U Davis Davis, Cal.	C72-2945	000	6-25-72 to 6-24-73	399,000 399,000**	(M00)	Borhani, Nemat
Michigan University Ann Arbor, Mich.	C72-2018	000	9-01-71 to 12-31-71 0- 0- 0 to 0- 0- 0 1-01-72 to 2-29-72	16,186 000 000 16,186**	(M00) (M01) (M02)	Epstein, Frederick H.
*** Minnesota University Minneapolis, Minn.	C72-2971	000	6-28-72 to 6-27-73	199,500 199,500**	(M00)	Kjelsberg, Marcus O.
*** Minnesota University Minneapolis, Minn.	C72-2976	000	6-28-72 to 6-27-73	370,700 370,000**	(M00)	Blackburn, Henry
***California U Davis Davis, Cal.	C72-2977	000	6-28-72 to 6-27-73	382,250 382,250**	(M00)	Borhani, Nemat D.
***Northwestern U Medical School Chicago, Ill.	C72-2978	000	6-28-72 to 6-27-73	390,590 390,590**	(M00)	Stamler, Jeremiah
***Harvard University Cambridge, Mass.	C72-2979	000	6-28-72 to 6-27-73	384,600 384,600**	(M00)	Dalen, J. E.
***Maryland U School of Medicine Baltimore, Md.	C72-2980	000	6-28-72 to 6-27-73	384,865 384,865**	(M00)	Warbasse, J. Richard
***Inst of Medical Sciences San Francisco, Cal.	C72-2981	000	6-28-72 to 6-27-73	385,470 385,470**	(M00)	Hulley, S.
***St. Louis Heart Association St. Louis, Mo.	C72-2982	000	6-28-72 to 6-27-73	384,475 384,475**	(M00)	Zimmerman, Herbert
***American Health Foundation New York, N.Y.	C72-2983	000	6-28-72 to 6-27-73	385,990 385,990**	(M00)	Wynder, Ernest L.
Chicago University Chicago, Ill.	C72-2923	000	6-25-72 to 6-24-73	95,000 95,000**	(M00)	Jones, Richard J.
Chicago Heart Association Chicago, Ill.	C72-2924	000	6-29-72 to 6-28-73	190,694 190,694**	(M00)	Mojonnier, Louise
			PROGRAM AREA TOTAL	$7,981,964		

*** Multiple risk factor intervention trial for the prevention of coronary heart disease

TABLE VII-F

National Blood Resources Program - Urokinase-Streptokinase-Pulmonary Embolism Trial January 31, 1973

Contractor	Number	Prior Funds	FY 72 Period	FY 72 Funds	MOD #	Principal Investigator
Colorado U School of Medicine Denver, Colo.	C68-1385	$ 74,980	5-01-72 to 10-30-72	$ 000 000**	(MO8)	Genton, Edward
Johns Hopkins University Baltimore, Md.	C68-1398	180,800	6- 0-71 to 5- 0-72 6-01-72 to 11-30-72 0- 0- 0 to 0- 0- 0	3,300 48,700 000 52,000**	(MO7) (MO8) (MO9)	Bell, William R.
Marshfield Clinic FDH Marshfield, Wis.	C68-1399	140,170	6-01-72 to 11-30-72	000 000**	(M11)	Sautter, Richard D.
Washington U Seattle Seattle, Wash.	C68-1429	273,282	6-28-72 to 12-27-72	29,700 29,700**	(MO8)	Blackmon, John R.
*New York University New York, N.Y.	C68-1507	113,317	6-19-72 to 12-18-72	31,044 31,044**	(MO6)	Johnson, Alan J.
Emory U School of Medicine Atlanta, Ga.	C69-2120	152,425	8- 0-71 to 9- 0-71 10- 0-71 to 10- 0-71 11- 0-71 to 9- 0-72	000 000 72,815 72,815**	(MO5) (MO6) (MO7)	Wenger, Nanette Kass
Michigan U Medical School Ann Arbor, Mich	C69-2121	114,480	8- 0-71 to 9- 0-71 9- 0-71 to 10- 0-71 10- 0-71 to 11- 0-71 11- 0-71 to 10- 0-72	000 000 000 69,408 69,408**	(MO6) (MO7) (MO8) (MO9)	Willis, Park W.
Mount Sinai Hosp of Gtr Miami Miami Beach, Fla.	C69-2122	$127,914	8- 0-71 to 9- 0-71	000 000**	(MO4)	Hildner, Frank J.
Texas U Medical Branch Galveston, Tex.	C69-2124	132,471	10- 0-71 to 10- 0-71 11- 0-71 to 12- 0-71 1-01-72 to 4-30-72 5-01-72 to 10-30-72	000 000 000 000 000**	(MO6) (MO7) (MO8) (MO9)	Cooley, Robert N.
Boston City Hospital Boston, Mass.	C70-2297	110,740	7-01-72 to 12-31-72	000 000**	(MO2)	Messer, Joseph V.
VA Hospital West Roxbury West Roxbury, Mass.	R69-0003	116,486	7- 0-71 to 6- 0-72	41,336 41,336**	(M53)	Sasahara, Arthur A.

*Central Reference Laboratory
**Total Contract Funding - FY 72

MEDICAL DEVICES APPLICATIONS PROGRAM,
BY PROGRAM AREA
(Tables VIII-A and VIII-B)

TABLE VIII-A

FY 72 Research Contracts Medical Devices Applications Program
by Program Area
January 16, 1973

	No.	Dollars
A. Biomaterials		
1. Research and Development	13	$ 805,879
2. Evaluation	2	94,165
	15	900,044
B. Artificial Heart		
1. Cardiac Assist	23	4,867,852
2. Total Heart	5	845,563
	28	5,713,415
C. Artificial Lung		
1. Pulmonary Assist	6	399,209
2. Total Lung	1	90,700
	7	489,909
D. Bioinstrumentation		
1. Diagnosis and Monitoring	3	251,386
E. Medical Devices Applications		
1. Test and Evaluation Facilities	2	2,405,317
F. Special Programs		
1. Auxiliary Devices	3	817,448
2. Technical Studies	2	7,000
	5	824,448
TOTAL PROGRAM	60	$10,584,519

TABLE VIII-B

FY 72 Operational Objectives*
January 22, 1973

F. Special Programs

Auxiliary Medical Devices

1. Initiate development and evaluation of implantable cardiac pacemaker with radioisotope or other energy sources;

2. Initiate development and testing of improved cardiac valves; and

3. Perform necessary oxygenator, blood pump, and other component fabrication to support overall program development and test programs as well as to establish standard techniques of production and quality control.

C71-2065	Fabrication of Implantable Artificial Heart Devices	Thermo Electron	$379,544
C71-2035	Fabrication of Implantable Artificial Heart Devices	Tecna	360,924
C71-2047	Fabrication of Artificial Heart Devices	Abcor	76,980
			$817,448

*Provided by NHLI, Division of Lung Programs

NATIONAL BLOOD RESOURCES PROGRAM,
BY PROGRAM AREA
(Table IX)

TABLE IX

FY 72 Research Contracts National Blood Resources Program
by Program Area
January 17, 1973

	No.	Dollars
A. Procurement and Distribution		
1. Operations Research Study of American Blood	1	$ 37,100
B. Blood Supply		
1. Oxygen Transport in Blood (2,3 DPG)	5	225,404
C. Hemophilia and Component Therapy		
1. Standardization of Cryoprecipitate	4	211,747
2. Blood Fractionation	1	17,624
3. Platelet Preservation	3	233,330
	8	462,701
D. Safety of Blood Therapy		
1. Detection of Hepatitis	8	775,692
2. Removal of Hepatitis from Blood	3	133,491
3. Histocompatibility Antigen-Poor Blood	4	180,830
4. Blood Donor-Recipient Identification	3	416,600
5. Distribution of HAA and Antibody for Educational Purposes	2	68,645
6. Hyperimmune Gamma Globulin Study	4	964,213
7. Epidemiology and Bioimmunology of HAA Carriers	4	558,745
8. Cytomegalovirus	6	429,700
9. Toxicology of Plastic Devices in Contact with Blood	3	321,340
	37	3,849,256
E. Thrombotic Diseases		
1. Urokinase--Pulmonary Embolism Trial	6	296,303
2. Pilot Study--Myocardial Infarction	1	66,480
3. Nonurinary Urokinase Production	2	374,363
	9	737,146
F. Sickle Cell Studies*		
1. Sickle Cell Disease Studies	27	1,662,715
2. Trial of Treatment for Sickle Cell Crisis	7	662,840
	34	2,325,555
G. Prenatal Diagnosis of Hereditary Blood Disease	4	192,700
TOTAL PROGRAM	98	$7,829,862

*The Sickle Cell Disease Branch had a reimbursable agreement with HSMHA for $1,975,000.

U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service
National Institutes of Health
National Heart and Lung Institute
DHEW Publication No. (NIH) 73–522

NATIONAL HEART, BLOOD VESSEL, LUNG AND BLOOD PROGRAM

VOLUME V
PROGRAM ANALYSIS

PART II

NATIONAL INSTITUTES OF HEALTH
EXCLUSIVE OF THE NATIONAL HEART AND LUNG INSTITUTE)

APRIL 20, 1973

U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service
National Institutes of Health
National Heart and Lung Institute

NATIONAL HEART, BLOOD VESSEL, LUNG AND BLOOD PROGRAM

VOLUME V
PROGRAM ANALYSIS

PART II

NATIONAL INSTITUTES OF HEALTH
(EXCLUSIVE OF THE NATIONAL HEART AND LUNG INSTITUTE)

APRIL 20, 1973

U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service
National Institutes of Health
National Heart and Lung Institute
DHEW Publication No. (NIH) 73–523

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402
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P R E F A C E

Volume V, Program Analysis, is a compilation of program information describing federally supported research efforts relevant to heart, blood vessel, lung and blood diseases and blood resources. The information presented is based on data from fiscal year 1972 (FY 72), the most recent period for which detailed program data are available. An exception is the program (discussed in Part III) of the Environmental Protection Agency for which FY 73 figures are given, since that is the first full year of Agency operation.

Volume V, Program Analysis, is presented in three parts:

Part I - National Heart and Lung Institute

Part II - National Institutes of Health (exclusive of the National Heart and Lung Institute)

Part III - Other Federal Agencies, (USDA, AEC, DOD, EPA, FDA, HSMHA, NASA, NSF, SRS, SSA, DOT, and VA)

Volume V was prepared by the National Heart and Lung Institute with the support and cooperation of the members of the Interagency Technical Committee (IATC) and their respective organizations. The Interagency Technical Committee on Heart, Blood Vessel, Lung and Blood Diseases and Blood Resources, is by law, "responsible for coordinating those aspects of all federal health programs and activities relating to heart, blood vessel, lung and blood diseases and to blood resources to assure the adequacy and technical soundness of such programs and activities and to provide for the full communication and exchange of information necessary to maintain adequate coordination of such programs and activities."

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APPENDIX

A.1 Activities Index by NIH Components

A.2 Summary Program Support Data

F O R E W O R D

This report is Part II of Volume V, Program Analysis, of the National Heart, Blood Vessel, Lung and Blood Program. Summarized herein are the activities related to heart, blood vessel, lung and blood diseases and blood resources supported by organizational components of the National Institutes of Health (NIH), exclusive of the National Heart and Lung Institute (NHLI). These components are:

- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD)
- National Cancer Institute (NCI)
- National Institute of Dental Research (NIDR)
- National Institute of Environmental Health Sciences (NIEHS)
- National Eye Institute (NEI)
- National Institute of General Medical Sciences (NIGMS)
- National Institute of Child Health and Human Development (NICHD)
- National Institute of Neurological Diseases and Stroke (NINDS)
- Fogarty International Center (FIC)
- Bureau of Health Manpower Education (BHME)
- National Library of Medicine (NLM)
- Division of Research Resources (DRR)

The activities documented in this report are categorized into 38 major problem areas corresponding to the problem areas (excluding Education in Lung Diseases) considered by the four advisory panels and their task groups in their contribution to the National Heart, Blood Vessel, Lung, and Blood Program. Within each major problem area (e.g., Atherosclerosis), the research activities, exclusive of intramural programs, sponsored by all components of NIH in fiscal year 1972 (FY 72) are described.

Figure 1 depicts the focus of activities of each NIH component as related to the National Heart, Blood Vessel, Lung and Blood Program. In FY 72, the National Institutes of Health (exclusive of NHLI) sponsored related research, exclusive of intramural programs, at a level in excess of $50,000,000 (See Appendix).

An explanation of data sources and data presentation formats and conventions is presented here to clarify characteristics of this report for the Reader:

- Data Sources. Figure 2 depicts and describes the sources of information for data presented in this report.
- Data Formats and Conventions:
  - The percent (%) symbol which frequently follows funding data in Sections I through IV of this report indicates that dollar totals presented are based on dollars assigned (in the CRISP system) to a project(s) which is a component of a larger project. For example, if one of five components of a $100,000 program project grant is relevant to the National Program, then a funding level of $20.000

FIGURE 1

Summary Activities Perspective
(Related to the National Program)
National Institutes of Health

NIAID
The NIAID conducts and sponsors research on: microbiological and immunological involvement in cardiovascular and pulmonary function and disease, including rheumatic fever, endocarditis, glomerulonephritis, emphysema, nonallergic asthma and sarcoidosis; immunohematology; and immunosuppression in organ and tissue transplantation and lung infections.

NIAMDD
The NIAMDD conducts and sponsors research on: hematological diseases including anemias and thalassemias; connective tissue diseases of heart and blood vessels; lipids and lipoproteins; fluid and electrolyte balance; metabolism and nutrition and life cycle of blood elements; and cystic fibrosis and pulmonary alveolar proteinosis.

NCI
The NCI conducts and sponsors research on: tumors affecting coagulation mechanisms or cardiovascular and pulmonary regulation; transplantation and blood resources fractionation, preservation and utilization.

NIDR
The NIDR conducts and administers research on: oral microvasculature; tissue compatibility properties of biomaterials; collagen synthesis and degradation; immunological mechanisms and transplantation genetics.

NIEHS
The NIEHS conducts and sponsors research on: the effects of agents at low concentrations acting over long periods; multiple agent synergisms; the modifying effects of variable physical and biological states within man on susceptibility to and course of disease induced by environmental agents; and long-term epidemiological studies of populations with unusual environmental experiences or unique morbidity and mortality experiences.

NEI
The NEI conducts and sponsors research related to: retinal vascular metabolism and circulation; ocular vascular dynamics; platelet aggregation in retinopathies; and corneal vascularization and preservation.

NIGMS
The NIGMS conducts and sponsors research on: biochemistry and biophysics of the cardiovascular system, the pulmonary system, and blood and its components, engineering of cardiovascular assist and repair devices, sociological aspects of heart and pulmonary disease; anesthesia, trauma, shock, and surgery for correction of cardiopulmonary disorders.

NICHD
The NICHD conducts and sponsors research on: cardiopulmonary involvement in fetal development and pregnancy, including toxemia; cardiovascular and respiratory diseases of the newborn(hyaline membrane disease), rheumatic heart disease, congenital defects and cardiomyopathies, cardiovascular complications in the perinatal period; hematologic disorders; and renal development of function.

NINDS
The NINDS conducts and sponsors research on cerebrovascular disorders (stroke) and neurological effects on the cardiovascular and pulmonary systems including hypertension and arrhythmia.

FIC
The FIC is responsible for the administration of Scientific Activities Overseas including the NIH Special Foreign Currency (P.L. 480) Program, Conferences and Seminars, International Fellowships, and Scholars in Residence Programs.

BHME
The BHME supports and administers training and education programs for health professionals and paraprofessionals.

NLM
The NLM conducts and supports the development of: publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources; and biomedical computer and communications systems to assist in research, medical education and health care delivery.

DRR
The DRR provides support to biomedical research institutions for noncategorical resources including: clinical research centers support; biotechnology resources; animal models; and general research support for multicategorical programs.

FIGURE 2

Data Sources

NIH COMPONENTS	INFORMATION SOURCES
NIAID NIDR NEI BHME-AH*	THESE NIH COMPONENTS PROVIDED THE INFORMATION PRESENTED IN THIS REPORT
NIAMDD NCI NIEHS FIC NLM BHME-NH*	DATA FOR THESE NIH COMPONENTS WAS OBTAINED FROM THE COMPUTER RETRIEVAL OF INFORMATION ON SCIENTIFIC PROJECTS (CRISP) SYSTEM MAINTAINED BY THE NIH DIVISION OF RESEARCH GRANTS, FROM THE SCIENCE INFORMATION EXCHANGE (SIE) OF THE SMITHSONIAN INSTITUTE, AND FROM SELECTED NIH PUBLICATIONS
NIGMS NICHD NINDS DRR	DATA FOR THESE NIH COMPONENTS WAS OBTAINED BOTH FROM THE COMPONENTS THEMSELVES AND FROM CRISP AND SIE

* BHME-AH IS THE DIVISION OF ALLIED HEALTH MANPOWER, BUREAU OF HEALTH MANPOWER EDUCATION

BHME-NH IS THE DIVISION OF NURSING, BUREAU OF HEALTH MANPOWER EDUCATION

($100,000 divided by 5) is shown followed by a percent (%) symbol. These dollar values are therefore cost approximations. As part of the continuing NHLI evaluation effort, these figures are presently undergoing verification.

- Funding levels presented without the percent symbol are either the total dollars for a research project (grant or contract) as provided by CRISP or funding data provided by the cognizant NIH component.

This report is presented in four sections and an appendix:

- Heart and Blood Vessel Diseases--outlines, in 11 major problem areas, the related activities of 13 NIH components
- Lung Diseases--presents, in 14 major problem areas, discussions of relevant activities of NIH components
- Blood Diseases--describes the relevant NIH activities related to seven major problem areas
- Blood Resources--outlines, in six major problem areas, the related activities of NIH components
- Appendix--presents a listing, for each NIH organizational component, of the major problem areas in which each agency sponsored activities and a table summarizing the level of support provided by all components in all problem areas.

I. HEART AND BLOOD VESSEL DISEASES

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I. HEART AND BLOOD VESSEL DISEASES

This section summarizes, in 11 categories, research activities (exclusive of intramural programs) supported in fiscal year 1972 (FY 72) by organizational components of the National Institutes of Health, exclusive of the National Heart and Lung Institute:

- Atherosclerosis (Section 1.1)
- Coronary Heart Disease (Section 1.2)
- Peripheral Vascular Disease (Section 1.3)
- Hypertension (Section 1.4)
- Stroke (Section 1.5)
- Congenital Heart Disease (Section 1.6)
- Rheumatic and Other Valvular Heart Diseases (Section 1.7)
- Cardiomyopathy (Section 1.8)
- Arrhythmia (Section 1.9)
- Cardiac Failure (Section 1.10)
- Shock (Section 1.11).

1.1 ATHEROSCLEROSIS

1.1.A Atherosclerosis--National Institute of Allergy and Infectious Diseases (NIAID)

No identified ongoing NIAID supported research activities are related directly to this area.

1.1.B Atherosclerosis--National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD)

The NIAMDD funds and administers research related to this area (FY 72: 30 grant supported studies, totalling $1,586,176--%).

Among these studies are the following investigations:

- A Study of the Interrelationships Between Arteriosclerosis, Hyperlipidemia, Diabetes and Hypertension. This study is one of a multifaceted investigation conducted under a categorical clinical research center grant.

- A Study of the Prevention of Premature Atherosclerosis with Hyperlipidemic Drugs. (See above for appropriate topic description. This investigation is conducted under the same clinical research center grant.)

- A Study of Plasma Triglyceride and Lipoprotein Lipase. The overall purpose of the project is to understand, in molecular terms, the role of the enzyme, lipoprotein lipase, in the control of plasma triglyceride levels in mammals. The initial key process in directing the flow of circulating triglyceride from the plasma into various tissues is the hydrolysis of lipid by this enzyme. One study is concerned with the purification of lipoprotein lipase from heart and adipose tissues, determination of its properties, and preparation of

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antibodies to the "purified" protein. Simple *in vitro* systems, adipose, heart, and aorta tissues, and cells isolated from these tissues will be used to study factors regulating the synthesis of the enzyme, its release from cells, activation in or by tissue, and possible binding to capillary endothelial cells.

The various subspecies of lipoprotein lipase will be studied with regard to kinetic regulation by serum protein factors and heparin. Also, the effects of diet and actinomycin on these species will be determined. These characteristics will be related to enzyme isolated from cells, from incubation medium of cells and tissue, and from post-heparin plasma to locate the morphological site in the tissue from which each species is derived. Further, attempts will be made to locate lipoprotein lipase precisely within heart and adipose tissue at the electron microscopic level using peroxidase labelled antisera. With an understanding of these normal mechanisms, the change in regulatory factors in pathological states would be examined, specifically in conditions in which plasma triglyceride levels are elevated or where triglyceride deposition is abnormal.

- A Study of the Turnover and Metabolism of Cholesterol. This study is part of a larger project, the general goal of which is the acquisition of fundamental information about the metabolism of vitamin A, vitamin D, and cholesterol and the application of such knowledge to the study of human biology and disease. Research in cholesterol metabolism is involved in the examination of turnover of cholesterol in patients with hyperlipoproteinemia in order to quantitatively describe the parameters of cholesterol metabolism in patients with different types of hyperlipoproteinemia. The effects of therapy for hyperlipidemia are also being investigated.

- A Study of Lipid Metabolism and Function. This investigation involves a study of the significance of the *in vivo* sulfation of cholesterol by ascorbic acid 3-sulfate, the development of an analytical method to quantitate ascorbic acid 3-sulfate in tissues, and an investigation of the influence of administered ascorbic acid 3-sulfate on atherosclerotic experimental animals.

- A Study of Regulatory Mechanisms in Lipid Metabolism. The objectives of this project include the description of mechanisms for regulation of metabolism of lipids and lipoproteins by the liver; the description of the role of the liver in the synthesis, maintenance, and catabolism of blood lipids, including the obtaining of some insight into control mechanisms at the molecular and enzymatic level; and an investigation of the properties of serum lipoproteins (isolated by zonal ultracentrifugation) from normal man and other species, and from the human afflicted with various hyperlipemias, endocrine disorders and/or cardiovascular diseases.

1.1.C Atherosclerosis--National Cancer Institute (NCI)

No identified ongoing NCI supported research activities are related directly to this area.

1.1.D Atherosclerosis--National Institute of Dental Research (NIDR)

The NIDR funds and administers a program of research related to this area (FY 72: 17 grants, totalling $296,494).

These investigations of the microvasculature of the tooth pulp and periodontal tissues may contribute to the fundamental knowledge base related to this area. See Section 1.3.D for listing of related projects.

1.1.E Atherosclerosis--National Institute of Environmental Health Sciences (NIEHS)

In FY 72, NIEHS funded and administered one program project ($258,844) related to atherosclerosis entitled, Environmental Quality--Effects on Disease Processes.

The purpose of this research is to develop a system for the continuous exposure of experimental animals to various levels of complex mixtures of air pollutants for extended periods of time. Since it is likely that the excess mortality in human populations exposed to episodic air pollution occurs in individuals with pre-existing disease, animals in which known disease models have been produced or are present spontaneously are being chronically exposed to the simulated polluted air and compared to comparable animals maintained under the same environmental conditions--except that the air will be filtered and free of known pollutants. Although the primary objective is to study effects on disease, any adverse effects of air pollution on relatively healthy animals will also be assessed since suitable control animals will be included for each disease model.

Disease models studied include (initially): 1) enzyme-induced emphysema, 2) spontaneous and renovascular hypertension, 3) dietary atherosclerosis and heart disease, 4) a combination of hypertension and atherosclerosis, 5) diabetes mellitus alone and in combination with atherosclerosis, and 6) alcohol-induced liver disease. Observations will be recorded on mortality, morbidity and selected physiologic and morphologic variables in an attempt to quantitate pollutant effects and to obtain basic information concerning pathogenetic mechanisms.

1.1.F Atherosclerosis--National Eye Institute (NEI)

The NEI funds and administers research related to this area. Among this research are the following:

- Retinal Vascular Metabolism (FY 72: $2,750)*. Included in this research project are a study of the metabolism of retinal blood vessels, both normal and diseased (e.g., diabetic, hypertensive, etc.) and a study of the response of retinal blood vessels to pharmacologic agents.

- Ultrastructural Study of Ocular Vascular Permeability (FY 72: $8,500)*. This study involves an electron microscopic investigation of permeability changes in ocular vascular tissues using horseradish peroxidase and myeloperoxidase--and the effects of drugs on aqueous formation, inflammation of the anterior segment and retinal and choroidal circulation.

- Retinal Circulation Times. (See Section 1.5.F for description of this project.)

- System Development to Study Ocular Vascular Dynamics (FY 72: $15,000)*. This research project has as its objective the improvement of televised fluorescein angiography videotaped for study and analysis of flow rates and vascular changes in normal and diseased fundus. Circulatory patterns are being studied as well as changes induced by photocoagulation (xenon arc, argon laser) and other forms of treatment.

- Development of Noninvasive Techniques for Estimating Retinal and Choroidal Blood Flow. (FY 72: one contract; no funding level available at time report was prepared.) The objective of this study is the development of clinically useful methods of

---

*Dollar totals represent approximate applicable percentage devoted to research in this project related to the National Plan, as estimated by NEI.

estimating the rate of effective or nutrient blood flow to the human retina and choroid from the retinal and choroidal circulatory system. Two types of instruments are being developed for measuring arteriole-venous oxygen differences in the retinal and choroidal blood vessels. The fundus is photographed through green and red filters, and microdensitometry is performed on the photographic films. This procedure yields an estimate of the oxygen saturation of hemoglobin in the particular blood vessel analyzed. A choroidal oximeter which uses photoelectric measurement of light reflected from the choroid is being refined. It will enable the operator to scan and to measure reflected light from small regions of retinal arteries and veins. The output of this measurement will be processed and the arteriole-venous oxygen differences calculated.

Presently, emphasis is placed on the following areas:

- Refinement of techniques already developed under contract for measurement of A-V hemoglobin saturation differences of retinal and choroidal vessels using photographic and on-line scanning oximeter methods

- Standardization and calibration of systems and testing techniques in animals and normal volunteers under various physiologic conditions.

1.1.G Atherosclerosis--National Institute of General Medical Sciences (NIGMS)

The Pharmacology-Toxicology Program, NIGMS, funds and administers research efforts related to this area.

These efforts include:

- A Pharmacology-Toxicology Program (FY 72: $37,900) which is devoted to a basic metabolic study of a hypocholesteremic pyridine (an analogue of chlorotrianisene). The substance in question, compound S, is one of a large number of compounds synthesized

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in the hope of retaining the hypocholesteremic effects of trianisene with minimal estrogenic activity. In the rat, but not in man or monkeys, the compound is highly effective in lowering blood cholesterol; it may be that the substance is metabolized to an active derivative in the rat but to an inactive derivative in primates. It may also be that the rates of absorption and tissue distribution differ. This study is designed to examine exhaustively the metabolism of this and similar derivatives in rats and monkeys. Ultimately its aim is to develop an effective compound with similar hypocholesteremic effects in primates and humans as a possible therapeutic agent.

- In addition one investigation conducted as part of NIGMS funded Center for Inherited Diseases (FY 72: $27,942--%) involves controlled tests of dietary, drug and exercise manipulation of a genetic predisposition to myocardial infarction in a large high-risk population with inherited hyperlipidemias.

- A large NIGMS supported research center (FY 72: $344,035) includes a small research effort devoted to the continuing evaluation of the effects of selected hypolipidemic drugs and other pharmacologic agents on the kinetic analysis of cholesterol and triglyceride metabolism.

1.1.H Atherosclerosis--National Institute of Child Health and Human Development (NICHD)

NICHD funded and administered a program project related to atherosclerosis (FY 72: one grant, $215,933).

- Mechanisms of Cellular Aging and Degeneration. This program project includes three individual projects. The section most relevant here is Subcellular Events in Arterial Disease. This is a study of the atherosclerotic process in the rabbit. Smooth muscle cells have been isolated from the aorta of both normal and cholesterol-fed rabbits and successfully fractionated.

The lysosomes have been characterized and shown to undergo remarkable changes as a result of cholesterol feeding. Liposomal enzyme activities are increased three to tenfold in severely antheromatous arteries, which were found to contain a new population of lysosomes of very low density, rich in cholesterol and presumably other lipids. Plans call for future analysis and characterizations of these lysosomes, especially with respect to their lipid composition and cholesterol esterase activity.

1.1.I Atherosclerosis--National Institute of Neurological Diseases and Stroke (NINDS)

No identified ongoing NINDS supported research activities are related directly to this area.

1.1.J Atherosclerosis--Fogarty International Center (FIC)

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

1.1.K Atherosclerosis--Bureau of Health Manpower Education (BHME)

No identified ongoing BHME supported manpower activities are related directly to this area.

NHLI

1.1.L Atherosclerosis--National Library of Medicine (NLM)

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of National Heart and Lung Institute (NHLI):

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

1.1.M Atherosclerosis--Division of Research Resources (DRR)

The DRR provides support for noncategorical resources to biomedical research institutions in support of categorical research activities of NIH.* DRR supports programs in four basic areas:

- General Clinical Research Centers Program. This program supports discrete clinical units (usually in university or university affiliated hospitals), which are utilized in the conduct of multicategorical clinical research.
- Biotechnology Resources Program. This program supports the development and operation of large and complex technological resources (e.g., computer systems, electron microscopy service laboratories, mass spectrometry and nuclear magnetic resonance systems) for their application to biomedical research problems.

* DRR funds resources which contribute to performance of studies documented in each DRR section.

- Animal Resources Program. This program provides support for the development and improvement of various animal models, including non-human primates for use in biomedical research as well as the upgrading of institutional animal resources.

- General Research Support Program. This program provides general research support to health professional and university graduate schools and other biomedical research organizations. (This program, in FY 72, derived its funds from separate appropriations to the NIH and the NIMH; however, it was administered by DRR.)

In FY 72, DRR supported three biotechnology resources program grants and one animal resource grant, the relevant components of which were (FY 72: $66,430--%):

- Physiological regulation of lipid metabolism
- Mass spectra data (lipids)
- Metabolic models related to diabetes and atherosclerosis
- A resource for the study of atherosclerosis and glomerulonephritis in squirrel monkeys.

In FY 72, DRR funded and administered 25 general clinical research center grants with 43 relevant research components (FY 72: $712,775--%). These studies included:

- Effects of exercise on blood lipids
- Lipid metabolism studies
- Hyperlipemia and hyperlipidemia studies
- Relation of hyperlipemia to atherosclerosis
- Platelet cholesterol turnover in type II cholesterolemia

NHLI

- High carbohydrate diet in hypertriglyceridemia
- Effect of weight gain and loss on serum lipids and hyperlipemia
- Cholesterol overload--mechanism and correction
- Computer simulation of arterial pulse wave propagation
- Atherosclerosis and stress
- Cardiovascular changes in obesity
- Lipid metabolism of the fetus
- Hyperlipidemia in childhood
- Surgical therapy in arteriosclerosis
- Cerebral circulation in atherosclerosis.

1.2 CORONARY HEART DISEASE

1.2.A Coronary Heart Disease--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

1.2.B Coronary Heart Disease--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported research activities are related directly to this area.

1.2.C Coronary Heart Disease--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

1.2.D Coronary Heart Disease--National Institute of Dental Research

The NIDR funds and administers research related to this area (FY 72: 5 grants, totalling $162,977).

This NIDR funded research, while dealing with transplantation and implantation of teeth and prosthetic devices in the oral cavity copes with problems similar to those of artificial devices and transplantation in advanced stages of coronary heart disease and cardiac failure.

Among these NIDR funded studies are:

- Tissue Compatibility and Properties of Biomaterials (FY 72: $11,798).
- Ceramic-Metal Composites for Biomedical Applications (FY 72: $59,647).

1.2.E Coronary Heart Disease--National Institute of Environmental Health Sciences

In Fy 72, NIEHS funded and administered one research grant related primarily to coronary heart disease (FY 72: $37,532).

- Carbon Monoxide and Cultured Heart Cells. The objectives of this research are to determine the effects and the mechanism(s) of action of carbon monoxide and of hypoxia on the lipid disposition of cells cultured from neonatal rat hearts. Separate cultures of endothelial cells and beating muscle cells will be studied to determine the relative susceptibility of each. Effects to be studied include: lipid synthesis and cholesterol uptake, to be measured by the use of labeled compounds and cytochemistry; and changes in enzymes and respiratory carriers, to evaluate certain potential mechanisms.

For description of additional related research activities supported by NIEHS, see Section(s) 1.1.E and 2.2.E (paragraph on A Program in Environmental Physiology and Toxicology).

1.2.F Coronary Heart Disease--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

1.2.G Coronary Heart Disease--National Institute of General Medical Sciences

The NIGMS funds and administers research related to coronary heart disease.

Among this research are:

- A Program Project of Biomedical Research For the Critically Ill (FY 72: 1 grant, totalling $238,000). This project involves the development of a patient monitoring system for the critically ill. Such a system could be utilized in following the medical progress of coronary patients.

- A Study of Myocardial and Body Metabolism in the Critically Ill (Human) (FY 72: 1 contract, totalling $53,258). Possible correlations of energy metabolism to the state of the circulation (cardiac output, arterial pressure, systemic resistance) are being investigated in critically ill patients after cardiac surgery and myocardial infarction.

- Natural History of Heart, Cancer, and Stroke in a Population (FY 72: 1 grant, totalling $27,683--%). This component of an NIGMS supported program project involves studies of incidence, prevalence mortality rates, secular trends, prognosis and survival for disease entities and syndromes. This includes the incidence, risk factors and outcome of ischemic heart disease and stroke.

- A Program Project (FY 72: 1 grant, totalling $370,000). This involves a variety of studies some of which are related to cardiovascular functioning, including development of cardiac catheter-tip transducers for pressure and flow. Approximately one-third of the studies are in the cardiovascular area.

1.2.H Coronary Heart Disease--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

1.2.I Coronary Heart Disease--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

1.2.J Coronary Heart Disease--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

1.2.K Coronary Heart Disease--Bureau of Health Manpower Education

The Division of Allied Health Manpower funds and administers programs related to this area (FY 72: 2 grants, totalling $95,260).

- Cardiovascular Technician Training Program. This is a 2-year program of formal training of high school graduates as cardiovascular technicians. Additionally, a 6-month training program in cardiovascular laboratory techniques has been developed for allied health professionals trained in other fields.

- Master Life Support Systems Technology Base. This program is designed to broaden an established program in anesthesia technology to develop the master life support technologist--providing a greater mobility and facility in the areas of emergency care, intensive care patient monitoring, respiratory care, post-trauma patient care, fetal monitoring and infant post-trauma resuscitation.

1.2.L Coronary Heart Disease--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases

- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

1.2.M Coronary Heart Disease--Division of Research Resources

DRR funds and administers biotechnology resources program grants and general clinical research center grants which have components relevant to coronary heart disease. (See Section 1.1.M for general description of DRR activities.)

In FY 72, DRR supported four biotechnology resources program grants which contained 11 related research components (FY 72: $153,858--%) entitled:

- Antemortem internal diameters of arteries
- Mapping of ischemic myocardial injury
- Long-term effects of coronary bypass grafts
- Postoperative monitoring of cardiac surgery patients
- Analysis of physiological data from infarct patients
- Exercise and clofibrate and coronary heart disease
- Angina pectoris diagnostics
- Ambulatory patient ECG
- ECG processing system development
- Cardiac ejection fraction
- Video display for surgical intensive care

In FY 72, DRR supported 25 clinical center grants in which 42 research components (FY 72: $567,527--% were related to coronary heart disease. Examples include:

- Studies of surgery for coronary disease
- Long-term hemodynamic changes after myocardial infarct
- Myocardial function and coronary artery anatomy after myocardial infarct
- Diagnosis of ischemic heart disease
- Metabolic abnormalities in premature coronary heart disease

NHLI

- Coronary vasodilator studies
- Surgical revascularization of ischemic myocardium
- Oxyhemoglobin dissociation curves in ischemic heart disease
- Nitroglycerin in genesis of coronary artery disease
- Evaluation of alprenolol in angina pectoris
- Physiologic responses in angina pectoris.

1.3 PERIPHERAL VASCULAR DISEASE

1.3.A Peripheral Vascular Disease--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

1.3.B Peripheral Vascular Disease--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported research activities are related directly to this area.

1.3.C Peripheral Vascular Disease--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

1.3.D Peripheral Vascular Disease--National Institute of Dental Research

The NIDR funds and administers research related to this area. These investigations of the microvasculature of the tooth pulp and periodontal tissues may contribute to the fundamental knowledge base related to this area. Among these investigations are:

- A study of circulation in teeth and supporting structures
- A study of systemic factors on circulation in oral soft tissues

- A study of the microvascular effects of biochemically insulting the crevicular epithelium
- A study of distribution and dynamics of blood flow in gingiva
- A study of the ultrastructure of diabetic gingival vasculature
- A study of growing capillaries--basal lamina and permeability.

1.3.E Peripheral Vascular Disease--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

1.3.F Peripheral Vascular Disease--National Eye Institute

The NEI funds and administers research related to this area.

- Retinal Vascular Metabolism. (See Section 1.1.F for description of this project.)
- Ultrastructural Study of Ocular Vascular Permeability. (See Section 1.1.F for description of this project.)
- Retinal Circulation Times. (See Section 1.5.F for description of this project.)
- Systems Development to Study Ocular Vascular Dynamics. (See Section 1.1.F for description of this project.)

NHLI

- Development of Non-Invasive Techniques for Estimating Retinal and Choroidal Blood Flow. (See Section 1.1.F for description of this project.)

1.3.G Peripheral Vascular Disease--National Institute of General Medical Sciences

The Biomedical Engineering Program, NIGMS, funds and administers one program project (FY 72: one grant, totalling $220,000) for the application of integrated electronics to biomedical problems. This includes a subproject on the development of a series of blood flowmeters (these studies constitute about one-third of the overall program). The flowmeters developed are already being used in cardiovascular surgery.

1.3.H Peripheral Vascular Disease--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

1.3.I Peripheral Vascular Disease--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

1.3.J Peripheral Vascular Disease--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health.

It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

1.3.K Peripheral Vascular Disease--Bureau of Health Manpower Education

The Division of Allied Health Manpower funds and administers programs related to this area (see Section 1.2.K for description of these projects).

1.3.L Peripheral Vascular Disease--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

1.3.M Peripheral Vascular Disease--Division of Research Resources

IN FY 72, DRR supported seven clinical center grants in which eight research components (FY 72: $121,110--%) were related to peripheral vascular disease:

- Vascular disease of the abdomen (human)
- Effect of beloxamide on atherosclerosis obliterans of lower extremities (human)
- Indirect effect of arterial narrowing (human)
- Evaluation of blood flow in lower extremity of arteriosclerosis obliterans (human)
- Acute peripheral arterial and venous occlusions (human)
- Arterial vasoplastic disorders of extremities (human)
- Effects of induced hypotension on peripheral circulation (human).

1.4 HYPERTENSION

1.4.A Hypertension--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

1.4.B Hypertension--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area (FY 72: 12 grants, totalling $549,605--%).

Among these studies are the following:

- A Study of Sodium Secretion in Hypertension, (FY 72: $20,457--%). This study is one of several investigations conducted in an NIAMDD funded clinical research center grant (a clinical metabolic research unit).
- A Study of the Control of Uric Acid Excretion in Essential Hypertension (FY 72: $16,949--%). This study is one part of an NIAMDD funded program project in nephrology. Areas covered by this program project include:
  - The functional capacity of the chronically diseased kidney within the experimental animal
  - Renal function in the presence of a reduced nephron population in man
  - Renal function in hypertension, with an emphasis on studies of intrarenal hemodynamics and renin secretion

- Renal pharmacology in the dog utilizing micropuncture and chronic renal artery catheterization techniques, particularly to investigate the influence of vitamin D metabolites on phosphate transport

- Renal pharmacology of lithium in man

- Studies of the basis for diuretic therapy in human diabetes insipidus utilizing the rat with hereditary diabetes insipidus

- New techniques of kidney preservation and utilization of human perfused kidneys for pharmacologic and metabolic studies

- Immunologic mechanisms in human glomerulopathies and their modification by therapy

- Metabolic consequences of uremia emphasizing isolation and characterization of uremic toxins and their inhibitory effect on transport, and the role of abnormal vitamin D metabolism in the pathogenesis of renal osteodystrophy

- Studies of renal metabolism in health and disease.

- A Study of the Metabolism of Antidiuretic Hormone (FY 72: $29,152). This study is involved in:

  - Increasing the accuracy and sensitivity of a bioassay method for ADH in the ethanol-anesthetized, water-loaded rat

  - Establishing the use of Share's method for extraction of vasopressin from the plasma when the concentration is near the physiological range.

  Once these procedures are satisfactorily working, total clearance and the renal hepatic and other regional clearances of vasopressin will be measured in rats and dogs under nearly physiological conditions.

- A Study of the Regulation of Sodium Excretion (FY 72: $66,423). This grant supported study is involved in an investigation of the multiple mechanisms that regulate sodium excretion. Attention is being focused on renal hemodynamic and physical factors which influence overall renal tubular sodium reabsorption and sodium excretion. Techniques employed include clearance studies in the dog and completely isolated dog kidneys, micropuncture techniques in the rat, perfusion studies in the rat intestine, and clearance studies in man. Parameters which are being investigated for a role in regulating tubular and gut sodium reabsorption include plasma protein concentration, renal vascular resistance, total blood flow, perfusion pressure, cardiac output, the hematocrit, and circulating vasoactive substance In addition, the effect of these physical and hemodynamic variables on the tubular transport of other species (glucose, bicarbonate, etc.) is being investigated.

- A Study of the Relation of Salt Excretion to Renal Metabolism (FY 72: $44,540). This research project is designed to study the relationship between extracellular and intracellular medium sodium on the intermediary metabolism of rabbit renal cortex and medulla *in vitro*. The effect of sodium and potassium on oxidative metabolism of the outer medulla is designed to include studies of the effect of these ions on oxygen consumption and sodium-ATPase on outer renal medullary homogenates with particular reference to the energy sources for hyperosmotic sodium transport in the processes of urinary concentration and dilution. In the cortex the effects of ammonium on oxidative metabolic pathways are designed to investigate the specific metabolic role of ammonium in the process of urinary acidification.

  Studies are being conducted to determine the role of the renomedullary prostaglandins with particular reference to:

  - Mechanism of action of renomedullary prostaglandins in patients with essential hypertension

  - Intrarenal role of renomedullary prostaglandins in regulation of the distribution of renal blood flow between medulla and cortex

- The renal involvement of PGA and PGE compounds in their antihypertensive action

- Measurements of PGA and PGE compounds by radioimmunoassay in experimental and human essential hypertension to determine if a deficiency of these compounds is etiologically important in the establishment of the hypertensive state.

- Prospective Study of the Natural History of Diabetes Mellitus in the Gila River Indian Community. (No funding data were available.) The objectives of this study are:

  - To determine the prevalence and incidence of chemical and clinical diabetes mellitus among those 5 years of age and over on the Gila River Indian Reservation

  - To evaluate factors associated with the progression from prediabetic state to chemical diabetes mellitus and to clinical diabetes

  - To study the association between diabetes and rate of appearance and progression of vascular complications

  - To investigate the influence of tribe, age, obesity, parity, and other factors on changes in glucose tolerance and their relationship to diabetes mellitus.

  The vascular complications of diabetes mellitus are responsible for the majority of the morbidity and mortality associated with diabetes mellitus. The relationship of hypertension to retinopathy in the diabetic appears to represent an important factor in the pathogenesis or progression of retinopathy and one whose effect is potentially amenable to alteration by safe medical means.

  The observation of the close association of renal disease and retinal abnormalities suggests that factors influencing the progression of one of these complications might well influence the other. However, the presently applied methods of investigation for renal disease are relatively insensitive and

nonspecific, and it seems probable that the application of more quantitative, sensitive, and discriminating methods for the evaluation of renal function could lead to a better understanding of factors related to the development and progression of diabetic nephropathy.

The observation of a high prevalence of eye and kidney abnormalities in subjects with newly recognized glucose intolerance suggests that a more basic abnormality than simply hyperglycemia is responsible for the development of the vascular lesions.

1.4.C Hypertension--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

1.4.D Hypertension--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

1.4.E Hypertension--National Institute of Environmental Health Sciences

In FY 72, NIEHS funded and administered a program project entitled "Center for Environmental Toxicology." One research component of this investigated the environmental toxicology of minerals related to hypertension (FY 72: $39,798--%).

For description of additional related research activities supported by NIEHS, see Section 1.1.E.

1.4.F Hypertension--National Eye Institute

The NEI funds and administers research related to this area.

Among this NEI supported research are:

- A Study of the Retinal Circulation (FY 72: $16,200*). This study includes an investigation of retinal arterial and venous circulation, of mean circulation time and vascular reactivity in patients with cerebrovascular disease and renal hypertension, and of factors affecting retinal circulation.
- Retinal Circulation Times. (See Section 1.5.F for description of this project.)
- Ultrastructural Study of Ocular Vascular Permeability. (See Section 1.1.F for description of this project.)
- Systems Development to Study Ocular Vascular Dynamics. (See Section 1.1.F for description of this project.)
- Development of Noninvasive Technology for Estimating Retinal and Choroidal Blood Flow. (See Section 1.1.F for description of this project.)

1.4.G Hypertension--National Institute of General Medical Sciences

The NIGMS funds and administers grant supported research related to the area of hypertension.

* Dollar totals represent approximate applicable percentage devoted to research in the project related to the National Plan, as estimated by NEI.

Among the research projects supported by NIGMS are:

- A Study of Hypertension Control (FY 72: $24,510--%). The Pharmacology-Toxicology Program, NIGMS, funds and administers a large center grant which has one section devoted to the study of hypertension control. Satisfactory control of hypertension with guanethidine administered in the usual progressively increasing maintenance doses can take many days or even weeks. The pharmacokinetic studies with labelled guanethidine being undertaken by this group suggest a more rational means of administering the drug when blood pressure control is more urgently required. It was demonstrated that the elimination of guanethidine takes place from several pools; one of these, with a half-life of about 5 days, appears to reflect relief from the adrenergic neuron where guanethidine acts to lower blood pressure. The release of guanethidine from this pool by dexamphetamine and prevention of its entry into the pool by protriptyline provides strong evidence that this pool largely reflects that drug which is stored in adrenergic neurons.

  Thus, assuming the hypothesis that the base pool represents guanethidine within adrenergic neurons, the effects of the drug should be related to the amount of drug present in the pool with a long half-life. With this information it should be possible to give a loading dose of guanethidine and maintain its effects by replacing losses from the "neuronal pool." This pharmacokinetic study is part of a large program devoted to the investigation of basic drug actions and interactions which has as its aim a more rational approach to the use of drugs.

- Human Drug Metabolism and Toxicology Center Grant (FY 72: $14,043--%). This involves a broad clinical pharmacology program which among its studies includes:

  - Investigation of new antihypertensive drugs--clonidine and guancydine

- Investigation of new antihypertensive drugs--CP-12, 299-1, CL 1388R, Abbot 31699 and WY 8678

- Antihypertensive efficacy and excretion of guanethidine in patients.

- A Research Program in Clinical Pharmacology (FY 72: $12,533--%). This program includes:

  - A study of patient variability in reaction to antihypertensive drugs

  - Clonidine hydrochloride trials in hypertension.

1.4.H Hypertension--National Institute of Child Health and Human Development

In FY 72, NICHD funded and administered one program project and one research grant related to hypertension.

- Origin of Early Hypertension of Early Childhood (FY 72: $17,938--%). The effects of bacteriuria in influencing blood pressure levels 10 years after the first detected episode are being studied in a follow-up of the original population. This will give the first information on the natural history of bacteriuria with observations over a decade. Long-term studies of the effect of bacteriuria on the development of hypertension in large unselected populations, and studies on the pathogenesis of experimental pyelonephritis are in progress. Studies of the microbial flora of the female genital tract, in relation to prematurity are in progress including the development of methods for the isolation and identification of mycoplasmas in the urine. In the latter situation, strong evidence of an association between genital mycoplasmas and low birth weight has been found and is being further investigated

- Renal Circulation During Pregnancy and Toxemia (FY 72: $34,372). The project is concerned with measuring distributional renal blood flow in normal pregnant and preeclamptic dogs and women. The study

employs dogs with banded uterine arteries which, when allowed to become pregnant, develop toxemia. Renal blood flow distribution measurements with the Krypton-85 washout techniques are correlated with anatomic studies, blood pressure and sodium excretion. Nonpregnant animals are studied before and after intrarenal and systemic administration of aldosterone, progesterone or human chorionic gonadotropin. As a second phase of the investigation, renal blood flow distribution measurements on normal pregnant and preeclamptic women are to be done using the Xeron-133 washout.

1.4.I Hypertension--National Institute of Neurological Diseases and Stroke

The NINDS funds and administers research related to this area (FY 72: seven grants, totalling $267,875--%).

Included in the NINDS supported research in this area are:

- Cooperative Stroke-Hypertension Study. This is a grant supported controlled double blind cooperative study of cerebrovascular disease and hypertension, designed to determine whether treatment of mildly or moderately hypertensive stroke patients with an active antihypertensive agent will improve prognosis when compared with treatment with a placebo agent. (See Section 1.5.I for a more complete description of this project.)

- Catecholamines in Cerebrovascular Disorders Associated with Hypertension. A component study of a NINDS supported cerebrovascular center, the FY 72 level of funding for this study was $37,665. This particular project involves studying the relation of hypertensive state to patients with cerebral infarcts by measuring levels of catecholamines derived from the circulation as well as from nerve fibers innervating the blood vessels.

- The Clinical Signs of Toxemia of Pregnancy and Their Association with the Outcome of Pregnancy. (No available data as to support mechanism or funding level.) The Perinatal Research Branch, NINDS, funds and administers this project.

  The purposes of this study are to:

  - Define quantitative gradients of the clinical signs of toxemia of pregnancy based on the reports over the course of pregnancy in the Perinatal Research Branch study records

  - Measure the elective weights of the clinical signs of toxemia of pregnancy--hypertension, edema, proteinuria singly and combined in their association with birth weight, fetal, neonatal, and perinatal mortality

  - Define a cohort of cases as "pregnancies complicated by toxemia" in the Perinatal Research Study for further research in association with the long-term development of the children.

  The original (raw) data on hypertension, edema, proteinuria, and their combination, were studied at seven time-intervals in the course of pregnancy, controlled by race, age, and parity of the gravidae. Findings included:

  - Mean diastolic and systolic blood pressures decrease in early pregnancy.

  - From 28 weeks to term, the mean systolic and diastolic blood pressure rise gradually about 10mm Hg.

  - The changes in mean blood pressures are not affected by the presence or absence of edema, proteinuria, or their combinations.

  - In the study the mean blood pressures during pregnancy are not different by race.

  - The level of the mean diastolic and systolic blood pressure increases with the age of the gravida.

- The mean blood pressures are little affected by parity of the order I or more. Multiparae, however, have a higher mean blood pressure in all age groups than parae I or more.

- Fetal, neonatal, and perinatal mortality and prematurity rate increase systematically with higher systolic and diastolic blood pressure in pregnancies, with no edema and no proteinuria, with edema, with proteinuria, and with edema and proteinuria. Critical blood pressure cutoff points have been determined.

The first part of the study has demonstrated the adequacy (consistency and validity) of the clinical data available, the range of their variability at seven intersections in the course of pregnancy and their association with certain population characteristics (race, age, parity).

In the second part the occurrence, increase, decrease and an appearance in time of the clinical signs of toxemia is being studied in the course of the individual study pregnancies in association with the immediate and long-term outcome of pregnancy.

- Central Integration of Cardiovascular Activity. (See Section 1.5.I for description of this project.)

1.4.J Hypertension--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars,

International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

1.4.K Hypertension--Bureau of Health Manpower Education

The Division of Allied Health Manpower funds and administers activities related to this area. (See Section 1.2.K for project descriptions.)

1.4.L Hypertension--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery medical education, and biomedical research.

1.4.M Hypertension--Division of Research Resources

The DRR funds and administers biotechnology resources grants and general clinical research center grants which have components relevant to hypertension. (See Section 1.1.M for general description of DRR activities).

In FY 72, the DRR supported five biotechnology research grants, which had five related components (FY 72: $35,425--%).

In FY 72, the DRR supported 46 clinical center grants which had 119 related components (FY 72: $1,928,496--%).

Included among the supported activities were:

- Support of computer facilities as a part of the instrumentation for hypertension research
- Support of clinical research centers for developing and evaluating improved care for hypertensive patients. This category of grant in general provides facilities for inpatient clinical research in a small tightly controlled unit which has ready access to specialized laboratory facilities, multi-disciplinary scientists and specialists. Each research component is concerned with a particular aspect of the disease, for example:
  - Relationships of sodium uptake, blood pressure and renal failure
  - Hypertension in children
  - Vasoconstrictor effects on renal blood flow
  - Hemodynamics and endocrine patterns in hypertension
  - Effects of hypotensive agents on toxemia of pregnancy
  - Investigations of antihypertensive agents
  - Natural history of renal diseases
  - Blood pressure response in bilateral nephrectomy
  - Beta blockers in hypertension.

NHLI

1.5 STROKE

1.5.A Stroke--National Institute of Allergy and Infectious Disease

No identified ongoing NIAID supported research activities are related directly to this area.

1.5.B Stroke--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported research activities are related directly to this area.

1.5.C Stroke--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

1.5.D Stroke--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

1.5.E Stroke--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

1.5.F Stroke--National Eye Institute

The NEI funds and administers research related to this area.

Among this NEI supported research are:

- A Study of the Retinal Circulation. (See Section 1.4.F for description of this project.)

- Retinal Circulation Times (FY 72: $22,650). This research project involves the development of a cinematographic technique for recording retinal circulation dynamics; the determination of valid norms; the documentation of pharmacological effects; and the study of patients with cardiovascular, cerebrovascular and ocular vascular diseases.

- Systems Development to Study Ocular Vascular Dynamics. (See Section 1.1.F for description of this project.)

- Development of Noninvasive Techniques for Estimating Retinal and Choroidal Blood Flow. (See Section 1.1.F for description of this project.)

1.5.G Stroke--National Institute of General Medical Sciences

The NIGMS funds and administers grant supported research in this area (FY 72: three grants, totalling $96,866--%).

These research projects include:

- A Study of the Natural History of Heart, Cancer, and Stroke in a Population. (See section on coronary heart disease for project description.)

- An Anesthesia Research Program Project which among component subprojects includes studies of:

  - Effects of carotid endarterectomy on regional cerebral circulation

  - Regional cerebral blood flow in the normal and ischemic brain

  - Effects of anesthetics on cerebrovascular circulation

- The Diagnostic Radiology Program, NIGMS, funds and administers projects for the development and application of new knowledge and techniques for the improved

diagnosis of disease using ionizing and infrared radiation, radioisotopes, and ultrasound.

The development of medical thermography is an important contribution in the early detection of cardiovascular diseases. Sensitive scanning radiometers have been developed which make thermal pictures of the skin visible in two-dimensional heat pictures. These temperature changes have been found to be associated with changes in cellular activity or blood flow in such diseases as stroke.

1.5.H Stroke--National Institute of Child Health and Human Development

In FY 72, the NICHD funded and administered one contract and two program projects which had component investigations pertinent to this area. (These data were obtained from the CRISP system maintained by the Division of Research Grants.)

- Collaborative Study of Oral Contraception. This contract was concerned with cerebrovascular disorders and their relationships to contraceptives (FY 72: $68,750).

- Cerebral Infarction in the Gerbil--Developmental and Therapeutic Studies. This project component study is concerned with the effect of cerebrovascular disorders, cerebral occlusions and thrombosis on subsequent development (FY 72: $7,707--%).

- Cerebral Physiology (Human). This study is concerned with cardiovascular function and cerebral blood flow (FY 72: $34,829--%).

- Cerebral Physiology. This study deals with cerebrovascular problems occurring with advancing age (FY 72: $34,829--%).

1.5.1 Stroke--National Institute of Neurological Diseases and Stroke

The NINDS funds and administers research related to this area (FY 72: 58 grants, totalling $5,239,979--%; 2 contracts, $65,937).

Among the NINDS supported studies in this area are:

- A Cooperative Study of Acute Treatment of Ruptured Intracranial Aneurysms. It is anticipated that this study will determine which is the best of three possible methods of protecting a patient against recurrent bleeding episodes during a period of 14 days after an acute subarachnoid hemorrhage from a ruptured intracranial aneurysm. Patients will be grouped by:

  - Location of the aneurysm
  - The specific day the angiographic diagnosis is made after the last bleeding episode
  - Clinical condition of the patient

  Three treatments, randomly selected, are being tested as follows:

  - Drug-induced, controlled hypotension
  - Antifibrolytic agent epsilon aminocaproic acid (EACA)
  - Drug-induced, controlled hypotension plus EACA.

- Cerebrovascular Clinical Research Centers (FY 72: $4,214,711). This is a program of 16 centers which conduct coordinated clinical and basic research. Included within these investigations are studies of or focused on:

  - Randomized treatment of patients with transient ischemic attacks by carotid endarterectomy, anticoagulation, and supportive measures

NHLI

- Measurement of regional cerebral blood flow using Xenon^{133}

- Hypoxia and cerebral glucose metabolism

- Action of pharmacologic agents on coronary blood flow

- Genetics of cerebrovascular accidents

- Treatment of cerebral ischemia with vasoactive drugs

- Five-year survival in ischemic cerebral vascular disease

- Plasma renin activity in acute cerebrovascular disease

- Respiratory pattern disturbances in ischemic cerebral vascular disease.

Among studies conducted in these centers during FY 72 selected for description in this report are:

- Measures of regional oxygen consumption and regional blood flow in a series of 25 stroke patients. This investigation revealed that regional oxygen consumption is not greatly affected by disease, that regional cerebral blood flow is more markedly affected by disease, and that the side of the cerebral "fast flow compartment" is greatly affected by disease. These studies indicate that the brain circulation comprises a fast flow compartment which is highly labile in disease. This observation is now under intensive investigation.

- Studies which have attempted to relate the pathophysiology of regional cerebral blood flow in experimental animals to autoregulation and CO_2 reactivity. When radioactive microspheres were injected into the circulation supplying the brain, a loss in autoregulation was noted. The failure to increase the amount of microspheres passing through the cerebral circulation suggested that significant capillary dilatation did not take place under these experimental conditions. It is possible that the "non-nutritional flow" recorded by this method may be related to an

increased local pressure and more rapid transit through the capillaries which are not enlarged.

Studies designed to investigate the effects of CO_2 inhalation on cerebral blood flow also produce some valuable information pertaining to cardiac function. In this series 23 stroke patients (9 normotensive and 14 hypertensive) underwent clinical cardiohemodynamic and cerebral blood flow studies before, during, and after CO_2 inhalation. The study demonstrated that in the 9 normotensive patients, mean systemic arterial blood pressure increased during CO_2 inhalation. When CO_2 inhalation was discontinued, mean arterial blood pressure fell below the normal baseline pressure in approximately 50 percent of the patients. Heart rate increased and mean pulmonary arterial pressure rose in most patients during CO_2 inhalation. Cardiac output increased from normal baseline levels in most patients while total systemic vascular resistance showed no consistent pattern of change, although cardiac work consistently increased during CO_2 inhalation. In the 14 hypertensive patients, the same directional changes seen in the normotensive were observed during CO_2 breathing. The rise in blood pressure during CO_2 inhalation reached dangerous levels in hypertensive patients. The baseline cardiac output was below normal in 10 of the 14 hypertensive patients. In spite of a low baseline cardiac output, it increased in all patients during CO_2 inhalation and, in some patients, fell to below baseline following withdrawal of the CO_2. This posthypercarbia fall in cardiac output and systemic arterial blood pressure may lead to a decrease in cerebral perfusion pressure following discontinuance of CO_2. This phenomenon may actually produce an aggravation of cerebrovascular insufficiency. Similarly, CO_2 inhalation invariably produced a rise in pulmonary pressure. This may cause a problem in patients with stroke and cor pulmonale. Therefore, CO_2 inhalation should be used with great caution in such patients. Oxygen consumption figures during the increased cerebral blood flow were not changed.

- Another area which has attracted the scientific interest of experimentalists working in stroke research centers has been the possible contribution of thrombus formation to the clinical symptoms related to stroke. One technique employed to study in vivo thrombus formation is the use of an extracorporeal teflon arteriovenus shunt in rats. Hemostatis was studied in this system by making a fine pin hole in the wall of the teflon arterial venus micro shunt with the aid of a deFonbrune micromanipulator. Within a few seconds to a few minutes the bleeding from the hole stops, just as bleeding from an ear or forearm incision stops. At a magnification of 1,000 the hole is seen to fill rapidly with a compact platelet aggregate or hemostatic plug. The investigator concluded that some component of the vessel wall is essential to thrombus formation. Basement membrane and subendothelial collagen are considered to have significant thrombogenic roles. Tissue thromboplastin, ATP-ases and ADP from the vessel wall were also considered to be significant.

- The Natural History of Stroke. At the present time, patients admitted to this study have just had a completed stroke. They undergo a complete evaluation which, in addition to the history, general physical examination, neurological examination and routine laboratory work, includes a variety of special studies such as the serum lipid profile, coagulation tests, angiography, aphasia tests, neurophysiological and neuropsychological investigations.

- Cooperative Stroke-Hypertension Study. This study, initiated in 1966, was designed to determine the efficacy of long-term antihypertensive therapy on the recurrence rate of stroke. In ambulatory patients with mild or moderate hypertension (i.e., this is a double blind study designed to determine whether treatment of mildly or moderately hypertensive stroke patients with an active antihypertensive agent will improve prognosis when compared to a placebo).

  The drug combination of methyl clothiazide and deserpedine was given in a double blind fashion to half the number of patients; a placebo was given to the other half of the study group. The data were randomized at a Central Registry.

NHLI

Eleven clinics and one Central Registry participate in this program. Four hundred and fifty-five stroke survivors have been registered during the study period.

Drugs and placebo categories have been specifically balanced with respect to race, sex, type of stroke and magnitude of blood pressure at randomization. Age, history of myocardial infarction, neurologic status, serum cholesterol, and diabetes have also been distributed equally between active drug and placebo groups. The study sample included 80 percent non-whites; 58 percent males; 77 percent single completed strokes; 50.6 percent diastolic blood pressure over 100mm Hg diastolic.

Based upon the study design, the close and uniform follow-up will make available precise data as to blood pressure response and rates for cerebrovascular accident recurrence and other morbidity. The collection of clinical data is now being concluded. During the forthcoming final year of the program, the data collected will be subjected to detailed analysis.

The data obtained are being processed for analysis and evaluation. Three major reports will be prepared for publication. The investigators from the various clinics are participating in the preparation of the final reports which will be concerned with:

- Outcome of stroke survivors under treatment as compared to those on placebo

- Effect of active therapy versus placebo on blood pressure, cardiovascular morbidity, and apparent drug toxicity

- Relationship of initial neurologic event to prognosis and to nature of stroke recurrence.

In addition, "spin-off" studies are under consideration by the participating clinicians who have special interests e.g., role of initial cardiovascular status on prognosis; long-term effect of treatment on fasting blood sugar; uric acid, electrolytes, electrocardiogram, etc.

- Experimental Cerebral Injury and Edema. This research project involves the production of focal areas of hemorrhagic necrosis in the brains of monkeys and dogs. The accompanying cerebral edema is studied by morphological and chemical means. Alterations in water, electrolytes and proteins in the brain are being defined and correlated with morphologic changes. The effects of therapy are to be studied, as are the effects of hypertension and hyperthermia.

- Innervation of Brain Arteries--EM--Cytochemical Studies. This research project involves the study of the autonomic innervation of intracranial arteries. An increasing body of evidence is accumulating that suggests that cerebral blood flow is regulated by or modulated by these neural influences. This study is concerned with the investigation of the structural substrate for such regulatory mechanisms--specifically, about the distribution and extent of the course of perivascular nerves on arteries within the brain parenchyma.

- Central Integration of Cardiovascular Activity. This research project focuses upon the elucidation of how and what influence supramedullary areas have on cardiac and vascular activity and further, how these neuro elements are modified by afferent information. Based on previous studies, the hypothesis used is that neural components above the dimesenteric junction contribute to both the static and phasic adjustments of the circulation. The control system regulating blood pressure, part of which is the carotid sinus reflex, is represented by a mathematical model which is used as a tool to assess the changes in baroreceptor reflex responses while stimulating or after removing parts of the central control. The experiment is designed to permit analysis of efferent components that alter vascular parameters not only at high and low carotid sinus pressure but also at intermediate points throughout the reflex; for example, the relative importance of active versus passive vasodilation in an isolated muscle bed with varying degrees of baroreceptor activity.

- Histamine and Vasomotor Regulation. This research project involves studies concerned with the role of

histamine in physiological and pathological hemodynamic control functions with particular emphasis upon neurogenic controls and sites of action of released neuromediator. Studies will continue to identify those factors precipitating histaminergic vasomotor responses and the neurophysiological characteristic of the transmission pathways.

- Exchanges Between Blood--Normal and Abnormal Brain. This research project deals primarily with different phases of ischemia. The project is designed to:

  - Identify what factors may substantially reduce the "no reflow phenomena" following total cerebral ischemia in rabbits

  - Establish total cerebral ischemia model for cats for survival experiments

  - Evaluate cerebral revascularization in the dog

  - Assess the effects of various medicinal treatments upon food cerebral ischemia and anoxia, specifically diphenylhydantoin, cycloheximide, and dibucaine.

- Neuroendocrine Mechanisms Controlling Organ Perfusion. This research project involves a continuing study of the ways in which circulating hormones, neurohumors and neurohormonal substances influence animal behavior and, in particular, how they integrate functions of organ systems by redistributing the cardiac output. Specifically this study concerns itself with how adrenal and sex steroids and catecholamines modify blood flow to various regions of the brain and other nervous system structures.

  A relatively simple and rapid method is employed permitting the measurement of nutritional (exchangeable) flow of blood through many areas of the nervous system at the same time in small laboratory animals without the use of anesthesia or restraint.

  The newly refined approach also is applicable to the study of neuroendocrine involvement in as wide a range of nervous system dysfunctions as cerebrovascular pathology and convulsions.

- Control of Cerebral Hemodynamics and Metabolism. This research project has as its basic objective an understanding of the control of cerebral circulation and metabolism in physiological and pathological states. An understanding of the normal workings of this control system should enable an intelligent study of the derangements in various pathologic conditions encountered in clinical neurology, in particular in cerebrovascular disorders. In addition, this information may serve as a rational basis upon which to plan effective therapeutic and preventive measures. Several approaches to understanding this control system have been initiated. They include an analysis of theoretical mathematical models describing cerebral clearance curves a study of mathematical models describing the transient responses to various factors that influence cerebral circulation and metabolism and the development of new techniques for measuring quantitatively regional cerebral blood flow and regional cerebral metabolism.

  These studies are being conducted in normal volunteers as well as patients with various neurologic disorders in order to gain some insight into the pathophysiology of these conditions.

- Epidemiological Research on Stroke. This program project involves four major independent, yet integrated studies:

  - An analysis of mortality due to cerebrovascular disease in California

  - Studies of precursors of cerebrovascular disease

  - A prospective study of mortality and morbidity in a free-living retirement community

  - A study of the characteristics of Japanese-Americans in California and their experience with cerebrovascular disease, coronary heart disease, and hypertension.

- Estimation of Cerebral Blood Flow by Xe^{133} Inhalation. The purpose of this research project is to test the clinical usefulness of an inhalation method for estimating fast compartment blood flow from extracranially monitored clearance curves (following one minute of

Xe^{133} inhalation). This technique, which is non-invasive, is potentially useful for serial determinations of regional cerebral blood flow in a variety of patients with hemodynamic disorders. Testing of the clinical usefulness of this technique involves collaboration with two NINDS funded cerebrovascular Research Centers.

- Epidemiology of Strokes. A continuation of one aspect of the NHLI-Framingham Heart Disease Epidemiology Study, this project is attempting to identify all subjects who have developed any manifestations attributable to cerebrovascular disease. This is being accomplished by clinical evaluation of all living subjects (approximately 4,200 men and women aged 52-82) and a detailed neurological evaluation of all subjects suspected of cerebrovascular disease. In addition, records pertaining to death and illness are being reviewed to ascertain in which subjects death can be attributed to cerebrovascular disease or in which any illness might be on the basis of cerebrovascular disease.

  Together with past data, accurate estimates of the incidence of the various manifestations of cerebrovascular disease can be made. Relationship of various host and environmental variables measured over the course of the entire study (21 years) will be studied to determine which factors relate to the development of stroke and transient ischemic attacks.

- Development of Methods of Blood Flow Measurements. (No data information available on funding mechanism or FY 72 level.) This project involves the development of a high resolution gamma detector system and a computer readout system. While developed primarily for use in the detection of mass lesions of the brain, this study also involves an exploration of the feasibility of its use in the measurement and accurate quantification of regional cerebral blood flow.

- Bibliographic Alerting and Retrieval Service on Cerebrovascular Disease. The Special Programs Branch, Collaborative and Field Studies, NINDS, funds and administers this contract supported project. The objective of this project is to provide a bibliographic alerting and retrieval service on cerebrovascular disease by

preparing abstracts of appropriate articles for publication in Stroke--A Journal of Cerebral Circulation (abstracts appear bimonthly).

- Study of Regional Differences in Stroke Mortality. Funded and administered by the Epidemiology Branch, Collaborative and Field Research, NINDS, this study has as its objectives to:

  - Analyze death certificates of all veterans dying in 1967 in Georgia (high mortality area) and five Rocky Mountain States (low mortality area). From the certificates approximately 1,000 certified CVA deaths in each area and 100 randomly selected controls would be chosen for further analysis (2,200 cases total). From these basic data, the frequency of reported CVA among veterans would be compared with male populations in similar areas to determine if the geographic variations reported for civilians occur among veterans.

  - Establish the validity of the diagnosis (by review of available hospital records and, when necessary, by physician or family interview) in order to estimate the relative frequency of mistaken diagnosis or failure to make the diagnosis of CVA.

  - Compile an estimate of the relative frequency of specific type of CVA (by a review of the accumulated information on veterans dying of CVA).

  - Analyze all verified stroke deaths and all errors in death certification--in terms of geography, age, race, place of residence, marital status, from the point of view of sources of information (competence of certifying individual) and other variables.

  - Review of the complete military and VA folders for a subgroup of 50 cases and controls per state in order to evaluate the usefulness of these records in subsequent studies. (In addition, an exploration of all other avenues of ascertainment of a valid rate of CVA among veterans in order that a definitive study of veterans population be conducted in the future when the great bulk of veterans of World War II arrives at the age of high risk for CVA.)

NHLI

A total of approximately 1,000 stroke deaths and 2,900 deaths from other causes has been compiled The data on these cases are analyzed. A preliminary review of the stroke cases in Georgia (which has a high mortality rate from stroke) versus the Rocky Mountain States (which have a low reported mortality from strokes) has revealed surprising and potentially important information indicating a pattern of greater risk in Georgia than the Mountain States and thus supporting previous observations.

1.5.J Stroke--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L.480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

1.5.K Stroke--Bureau of Health Manpower Education

In FY 72, the BHME Division of Nursing funded and administered one research grant relevant to stroke.

- Upper Extremity Positioning of Stroke Patients (FY 72: $95,628). This research is designed to study three objectives:
  - Determine if specific positioning measures prevent or minimize development of deformities in the affected upper extremity of the stroke patient
  - Observe three characteristics (age, type of stroke, dominant versus nondominant extremity) to see if treatment response appears to be influenced by these factors

NHLI

- Observe to see if any difference in treatment response is suggested by the two sexes.

The study will be a two-group experimental design, with stroke patients randomly assigned to Treatment One or Treatment Two groups. The design will be balanced by assigning the next patient with similar characteristics to the other Treatment group. A total of 72 patients will comprise the sample.

Data collection will be divided into four phases, three occurring in the hospital and one 8 weeks after discharge. Two techniques will be utilized:

- Protocol for positioning, and
- Protocol for measuring degree of motion in specific joints of the affected upper extremity.

A 2 x 2 x 3 x 2 factorial design with three observations per cell will be used to examine the main effects and interactions. In the event the investigator cannot randomize the available patients to accomplish a balanced design, a multiple covariance analysis will be performed

For description of additional related research activities supported by BHME, Division of Allied Health, see Section 1.2.K.

1.5.L Stroke--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

1.5.M Stroke--Division of Research Resources

The DRR funds and administers biotechnology resources grants and general clinical research center grants which have components relevant to stroke. (See Section 1.1.M for general description of DRR activities.)

In FY 72, the DRR supported four biotechnology resources grants which had seven related research components (FY 72: $33,742--8).

In FY 72, the DRR supported six general clinical center grants which had eight related research components (FY 72: $93,161--8).

The titles of these components, or the subject matter where there are several related components, are given below:

- Computer support in the evaluation of intensive care unit
- Computer support in studies of cerebral blood flow and microcirculation
- Computer support in rehabilitation studies
- Studies of cerebral vasodilators
- Abnormal carbohydrate metabolism in stroke
- Sleep studies in stroke
- Studies of intracranial aneurysms.

1.6 CONGENITAL HEART DISEASE

1.6.A Congenital Heart Disease--National Institute of Allergy and Infectious Diseases

In FY 72, the NIAID funded one grant in the amount of $44,264 to study the pathogenesis and teratogenesis of mumps virus and feline panleukopenia virus infections in the developing cat fetus. Attention is paid to transplancental transmission, the "blood brain barrier" and the immune response of the fetus to infection.

1.6.B Congenital Heart Disease--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported research activities are related directly to this area.

1.6.C Congenital Heart Disease--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

1.6.D Congenital Heart Disease--National Institute of Dental Research

The NIDR funds and administers research related to this area (FY 72: one grant, totalling $16,937--%).

- Cardiac Malformation in Humans and Animals with Craniofacial Birth Defects. This study is part of the program of an NIDR supported Center for Craniofacial Anomalies which is a multidisciplinary

organization concerned with the study and treatment of patients with congenital, developmental and acquired craniofacial defects.

1.6.E Congenital Heart Disease--National Institute of Environmental Health Sciences

A research component entitled "Teratology of Pesticides" of an NIEHS program project was directed at congenital abnormalities resulting from pesticide exposure (FY 72: $39,798--%).

In addition, NIEHS funded and administered three research projects (FY 72: $124,593) related to congenital heart disease. These were:

- Perinatal Pesticide Toxicity. Investigating congenital abnormalities in rats and mice
- Teratogenic Effects of Heavy Metals. Investigating the effect of biologically nonessential heavy metals on mammalian embryonic development
- Pesticide-Induced Change During the Perinatal Period. Directed toward the study of toxicity, teratogenecity, placental transfer and maternal, fetal and neonatal distribution of environmental toxicants.

1.6.F Congenital Heart Disease--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

1.6.G Congenital Heart Disease--National Institute of General Medical Sciences

The NIGMS funds and administers grant supported research related to this area (FY 72: 5 grants, totalling $324,084--%).

Among the applicable research projects are:

- The Development of New Transducer Systems. This study is a part of the program project "Biomedical Engineering Research for the Critically Ill," concerned with the development of patient diagnostic and support systems for pediatric patients. The area of congenital cardiac abnormalities is part of the primary emphases of this project.

- A Study of Diagnostic Content and Redundancy in Radiant Images: Measurement of Diagnostic Content. This program project is focused upon the automated diagnosis of disease through the use of the computers, and on measurement of intelligence content of radiant images. The area of congenital cardiac defects is among the primary emphases of this project.

1.6.H Congenital Heart Disease--National Institute of Child Health and Human Development

In FY 72, the NICHD funded and administered 8 research grants and 2 program project grants which had components pertinent to congenital heart disease (FY 72: $415,729--%).

- Mechanisms of Action of Chemical Teratogens (FY 72: $27,078). The uptake of 35S-labelled sodium sulfate is being used to measure the rate of mucopolysaccharide synthesis in the embryonic heart and limb. Experiments are being conducted, a) to demonstrate differences that may exist in such synthesis during normal and abnormal development and, b) to determine the susceptible biochemical reactions in the pathway of mucopolysaccharide synthesis.

Experiments are being conducted with this compound and nicotinamide in an effort, a) to determine how nicotinamide prevents the teratogenic action of thiadiazole and, b) to determine the site of action of thiadiazole.

- Studies of Multiple Congenital Abnormalities (FY 72: $51,430). Teratogens including trypan blue, methyl salicylate, retinoic acid, and dactinomycin are administered to pregnant rats in order to produce congenital abnormalities in the young. Each abnormality is studied from the early stages of pregnancy to birth in an attempt to understand more clearly the stages in its formation. Microscopic study, dissection, wax-plate reconstructions, and special stains are employed where appropriate. Attention is directed principally to malformations of the cardiovascular, urogenital, and nervous systems, and to those of the eye and face which have their counterpart in man.

- Congenital Malformations in Mammals (FY 72: $55,223). Congenital malformations are investigated in children by clinical, genetic and cytogenetic methods. Experimental teratology is practiced to supplement observations in children and to study pathogenesis and etiology of congenital malformations and related conditions of reproductive failure in animal models. In the past, mammalian experimental teratology was essentially limited to rodents; now it seems possible to obtain more meaningful models by the use of primates.

- Pathogenesis of Infection in Human Maldevelopment (FY 72: $59,643). The major objective is to determine the impact of infections, especially the "chronic," "slow" and ill defined forms on disturbances of normal development in man. Through serial microbiologic, serologic, immunologic and clinical study of the pregnant mother and her offspring, emphasis is placed on the role of the "chronic" intrauterine infections in production of disturbances of fetal development and malfunctions later in life. Insight into the pathogenesis of these disturbances is approached through detailed investigation of routes, transmission, effect of gestational age, antigenic variation amongst organisms and their relation to outcome of pregnancy, and nature of disease in the newborn. Similar longitudinal studies in infected

infants will be used to determine long-term effects of "chronic" intrauterine infections. In addition, newer biologic technics will be employed to investigate the viral etiology of severe debilitating CNS disease of infants and children, and in attempting to determine etiologic role of "slow" viruses in chronic disease of CNS and connective tissue of man.

- Experimental Methods of Teratogenesis (Rats, Monkeys) (FY 72: $90,518). The objectives are to utilize various embryopathic and teratogenic procedures in order to learn more about the factors that contribute to abnormal embryonic development. Interest is in determining the mechanisms whereby heterologous tetrogenic antisera, uterine vascular clamping and other embryopathic techniques interfere with embryonic development.

- Teratogenic Mechanisms in Mammals (Rats) (FY 72: $31,977). Drugs known to interfere with biosynthetic activity in mammalian cells are injected into pregnant rats on day 12 of gestation. One to 30 hours later a labelled precursor, either uridine, thymidine or leucine, is also injected, followed 2 hours later by surgical removal of one uterine horn. One embryo from the removed horn is prepared for histologic study and the remaining embryos are extracted for DNA, RNA or protein and the incorporated label measured and compared with control value to determine degree of interference with biosynthetic activity. The pregnant female is allowed to continue to the 20th day of gestation when fetuses in the residual horn are removed and examined for developmental abnormality. Mitotic activity and extent of cell death are evaluated in the sectioned embryos. Thus, by this "split-litter" technique it is possible to correlate cellular and molecular events in the embryo a few hours after treatment with the teratological and lethal effects seen in the 20-day fetus.

- Biochemical Events Preceding Birth Defects (Rats) (FY 72: $16,114). Normal and abnormal rat embryos are obtained from untreated and teratogen-treated mothers. Respiratory control and ADP:O ratios are being determined for mitochondria prepared from limbs and tails and torsos of these embryos. Mitochondrial preparations will be used also to determine in vitro

ATP:AMP phosphotransferase activity. Particulate subcellular fractions of normal and abnormal embryos will be assayed for distribution of isozymes of this enzyme. Mitochondria and particulate-free cytoplasmic extractions (cytosol) will be used in assaying for cytoplasmic control of mitochondrial function.

- The Nature of Growth in the Nonpubescent Child (FY 72: $35,253). This study deals with what constitutes growth for the nonpubescent child by measuring changes in total body fluids and electrolytes and body composition using four compartment analysis (fat and extracellular water, cells and bone), as they relate to anthropometric measurements (such as height, weight, assessment of leanness-fatness) and skeletal age. Studies done before surgery will assess the nature of the growth failure frequently seen. Such studies done in the postoperative period will fully assess the contribution of the various body compartments to growth as well as assess the time sequence at which increases in these various body compartments take place.

- Teratogenic Effects of Heavy Metals on Mammalian Embryo (Hamsters) (FY 72: $29,461--%). It is the purpose of the study to lead ultimately to a better understanding and approach to both prenatal and perinatal care in man, to improve genetic counselling, and to better understand basic mechanisms in mammalian reproduction and fetal development.

- Perinatal Radiology (Human) (FY 72: $19,032--%). One component of this project is concerned with congenital heart defects.

1.6.I Congenital Heart Disease--National Institute of Neurological Diseases and Stroke

The NINDS funds and administers research related to this area. (No funding data were available at the time this report was prepared.)

- An Investigation into the Relationship Between Congenital Heart and Great Vessel Anomalies and Selected Factors (as recorded in the collaborative perinatal project).

  The primary objective of this study is to assess relationships between certain maternal variables and congenital heart-great vessel anomalies.

  Additional objectives include investigating relationships between early signs of abnormality and the existence of definitive congenital heart lesions and determining the existence of congenital heart-vessel anomaly in conjunction with mental retardation as recorded in the 8-month psychological examination, the 1-year summary records, 4-year psychological examination, and 7-year neurological and psychological examinations.

  To date, maternal parameters analyzed included age of gravida, parity, prior pregnancy outcome, prior and current health status, ABO blood group, current smoking pattern, and viral antibody status.

  Study data were obtained from collaborative study records received by the Perinatal Research Branch from the onset of this study (January, 1959) through December, 1964. These records provide 112 live and stillbirth cardiac cases for study out of a population pool of approximately 38,000. Analysis of an expanded study cohort through 1965, with a population pool of approximately 55,000 providing additional cases, is underway in anticipation that the additional cases will support earlier findings and perhaps provide further clues for identifying etiological relationships.

  Preliminary analysis indicated that there was a definite preponderance of mothers over 30 in the C-V study group. Controlling for race, and removing cases with chromosomal aberrations, there were more white mothers in the 30-and-over age group than expected at the .05 level. This trend is also noted among blacks. There was a greater than expected number of gravida with systemic disease complications and prior pregnancy loss among the mothers of the cardiacs. A breakdown of these factors for greater specificity is pending.

Because the number of patients with each specific cardiac abnormality was small, specific associations between serological findings and clinical observations has not been possible, although several interesting trends have been noted. Analysis on the larger cohort is nearing completion.

1.6.J Congenital Heart Disease--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

1.6.K Congenital Heart Disease--Bureau of Health Manpower Education

For description of related manpower activities supported by BHME, Division of Allied Health, see Section 1.2.K.

1.6.L Congenital Heart Disease--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases

- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

1.6.M Congenital Heart Disease--Division of Research Resources

In FY 72, the DRR supported 2 biotechnology resource grants which had related research components (FY 72: $28,050--%), and 16 general clinical center grants which had 34 related research components (FY 72: $449,528--%).

Included among these efforts were:

- Computer support in studies of ventricular sepital defects
- Evaluation of congenital heart defects
- Studies of blood circulation dynamics in congenital heart disease
- Pediatric cardiology and surgery
- Pulmonary vascular impedance
- Hemodynamic effects of prosthetic valves
- Blood flow measurements in organs using isotopes
- Growth retardation
- Studies of teratogenic agents
- Angiographic studies of valvular regurgitation, shunt flow, left atrial volume.

1.7 RHEUMATIC AND OTHER VALVULAR HEART DISEASES

1.7.A Rheumatic and Other Valvular Heart Diseases--National Institute of Allergy and Infectious Diseases

During 1972 NIAID funded grants in this area totalling $238,989. Three of the awards were for study of the role of streptococci in the causation of rheumatic fever. The fourth supports an investigation of the role of staphylococcal toxins (cell poisons) in producing tissue lesions. In the streptococci investigations, major emphasis is placed on determining the chemistry and immunology of streptococcal antigens. The biology of group A streptococci and their relationship to the development of acute rheumatic fever and acute nephritis is being studied. There is some evidence that rheumatic fever may be a prototype for many illnesses where infection initiates an immune process detrimental to the host. Clarification of the abnormal immune state operative in rheumatic fever could lead to a better understanding of other such illnesses.

1.7.B Rheumatic and Other Valvular Heart Diseases--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported research activities are related directly to this area.

1.7.C Rheumatic and Other Valvular Heart Diseases--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

1.7.D Rheumatic and Other Valvular Heart Diseases--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

1.7.E Rheumatic and Other Valvular Heart Diseases--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

1.7.F Rheumatic and Other Valvular Heart Diseases--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

1.7.G Rheumatic and Other Valvular Heart Diseases--National Institute of General Medicine Sciences

No identified ongoing NIGMS supported research activities are related directly to this area.

1.7.H Rheumatic and Other Valvular Heart Diseases--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

1.7.I Rheumatic and Other Valvular Heart Diseases--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

1.7.J Rheumatic and Other Valvular Heart Diseases--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

1.7.K Rheumatic and Other Valvular Heart Diseases--Bureau of Health Manpower Education

BHME supports activities related to this area. (See Section 1.2.K for Master Life Support Systems Technology Base.)

1.7.L Rheumatic and Other Valvular Heart Diseases--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases

- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

1.7.M Rheumatic and Other Valvular Heart Diseases--Division of Research Resources

The DRR funds and administers biotechnology resources grants and general clinical research center grants which have components relevant to rheumatic and other valvular heart diseases. (See Section 1.1.M for general description of DRR activities.)

In FY 72, the DRR supported two biotechnology resources grants which had two related research components (FY 72: $10,089--%) and 11 general clinical center grants which had 14 related research components (FY 72: $317,625--%).

Included among these efforts were:

- Computer and mass spectrograph support of studies of cardiac valves
- Evaluation of myocardial function in valvular heart disease
- Cineangiographic studies
- Prosthetic heart valves
- Studies of valvular surgery
- Hemodynamic studies of valve disease
- Studies of rheumatic fever
- Studies of the effects of exercise.

1.8 CARDIOMYOPATHY

1.8.A Cardiomyopathy--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

1.8.B Cardiomyopathy--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area (FY 72: two grants, totalling $94,212).

The investigations related to this area are:

- A Study of Biochemical and Fine Structural Effects of Ethanol. This investigation involves studies of the mechanisms of pathologic effects produced by ethanol. Studies involve integrated biochemical and structural techniques, in experimental animals and man (in vivo and in vitro), to elucidate further the effects of ethanol on lipid and inter-metabolism in liver, adipose tissue, heart, and kidney. The effects of prolonged ethanol intake on proteins and lipoprotein metabolism and its role in the pathogenesis of alcoholic hyperlipemia is being studied. The effect of ethanol on ultrastructure of adipose tissue, heart, and kidney is to be assessed, and the amount, type, and origin of the lipids accumulated in the heart and kidney are to be assessed.

- A Study of Cell Permeability and Metabolism of Heart Muscle. This study is aimed at a determination of factors which influence the formation and degradation of intercellular heart lipids, in particular, the triglyceride fatty acids.

1.8.C Cardiomyopathy--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

1.8.D Cardiomyopathy--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

1.8.E Cardiomyopathy--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

1.8.F Cardiomyopathy--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

1.8.G Cardiomyopathy--National Institute of General Medical Sciences

The NIGMS funds and administers grant supported research related to this area (FY 72: five projects, totalling $324,084--%).

Among the applicable research projects are:

- Anesthesia Research Center Program (FY 72: $16,367--%). These program project studies include investigations of cardiac muscle mechanics at organ, tissue, and cellular levels.

- A Study of Myocardial Toxicity of Contrast Agents (FY 72: $32,929--8). This study is conducted at an NIGMS supported Diagnostic Radiology Research and Training Center.

1.8.H Cardiomyopathy--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

1.8.I Cardiomyopathy--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

1.8.J Cardiomyopathy--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program). Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

1.8.K Cardiomyopathy--Bureau of Health Manpower Education

No identified ongoing BHME supported manpower activities are related directly to this area.

1.8.L Cardiomyopathy--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

1.8.M. Cardiomyopathy--Division of Research Resources

The DRR funds and administers biotechnology resources grants and general clinical research center grants which have components relevant to cardiomyopathy. (See Section 1.1.M for general description of DRR activities.)

In FY 72, the DRR supported two biotechnology resources grants which had two related research components (FY 72: $9,963--%) and five clinical center grants which had six related research components (FY 72: $78,924--%).

These supported activities included;

- Provision of computer support in mathematical modelling of the myocardium
- Biopsy studies of myocardial disease
- Studies of therapy of cardiomyopathy and skeletal myopathy

- Studies of surgery on constrictive pericarditis
- Studies on the effects of bed rest
- Studies on the effect of ethanol
- Studies of familial hypertrophic myocardial disorders.

1.9 ARRHYTHMIA

1.9.A Arrhythmia--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

1.9.B Arrhythmia--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported research activities are related directly to this area.

1.9.C Arrhythmia--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

1.9.D Arrhythmia--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

1.9.E Arrhythmia--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

1.9.F Arrhythmia--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

1.9.G Arrhythmia--National Institute of General Medical Sciences

The NIGMS funds and administers grant supported research in this area (FY 72: seven grants, totalling $178,841--%).

Among the applicable NIGMS supported research projects are:

- A Study of Lidocaine in the Treatment of Arrhythmias (FY 72: $10,531--%). This study is conducted at a NIGMS supported Anesthesia Research Center as part of the center's broad-based, multidisciplinary research program which includes physiological and pharmacological studies of the circulatory system, effects of anesthetics and adjunct drugs, adrenergic agonists, and antagonists, arrhythmias and anti-arrhythmic drugs, and prostaglandins and their antagonists.

- Investigations of New Drugs--Cardiovascular Effect(s) of L-dopa (FY 72: $14,043--%). This study is conducted at a NIGMS supported research center for clinical pharmacology and drug toxicology.

- An Evaluation of Antiarrhythmic Drug, SU-13197 (FY 72: $24,510--%). This study is conducted at a NIGMS supported research center for clinical pharmacology and drug toxicology as a subproject.

- Development of Long-Term Energy Sources (FY 72: $90,000). These studies deal with the development of implantable biofuel cells, which--if and when developed--might be used to power cardiac pacemakers (among other uses for internal power sources).

1.9.H Arrhythmia--National Institute of Child Health and Human Development

In FY 72, the NICHD funded and administered one research

grant and a program project (which had one component) dealing with arrhythmia:

- A Study of Sudden and Unexpected Death in Infants (FY 72: $10,257). This research has as its objective the further study of lethal arrhythmias and conduction disturbances as a possible final common pathway in crib death. Anatomical studies are being performed to confirm the presence of focal patches of cardiac resorptive degeneration in portions of the AV node and the bundle of His, as observed by James (1968) in infants who have died suddenly and unexpectedly.

- Tolerance of Fetal Hearts to High Serum Potassium (FY 72: $39,255). The aim of this project is to study the phenomenon of the unusual tolerance of the fetal heart of small mammals to very high concentrations of potassium. This work grew out of observations made during studies of the biochemical and physiological changes in embryos subjected to teratological agents. Heart rate, heart irregularities and electrocardiograms are being followed in order to obtain further information about physiological alterations in the embryo during exposure to teratogens.

1.9.I Arrhythmia--National Institute of Neurological Diseases and Stroke

The NINDS funds and administers research related to this area (FY 72: three grants, totalling $104,723--%).

Among the NINDS supported research in this area is the following:

- Study of Related Cardiac Function (FY 72: $97,389). This study, part of an NINDS supported Center for Clinical Studies of Head Injury, relates to the area of cardiac function, specifically the

electrical activity of the heart. This project uses EKG's to provide a description and analysis of different dysrhythmias following head injury in patients and animal models. It is suggested that early dysrhythmias may be caused by vagal stimulation. This hypothesis is being tested by applying cholinergic blocking (atropine) in patients and vagal section in the animal models. β- adrenergic blockage will also be used in an effort to select out the responsible neurogenic drive, sympathetic or vagal, for the dysrhythmias. Ventricular function measurements will be done in patients, mainly with noninvasive methods and dye dilution cardiac output. The measurement of preejection/ejection period ratio, if done serially in the same patient and related to catecholamine levels, will give information regarding overall ventricular function.

- Central Integration of Cardiovascular Activity. (See 1.5.I for description of project.)

1.9.J Arrhythmia--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

1.9.K Arrhythmia--Bureau of Health Manpower Education

For description of related activities supported by BHME, Division of Allied Health Manpower, see Section 1.2.K.

1.9.L Arrhythmia--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

1.9.M Arrhythmia--Division of Research Resources

The DRR funds and administers biotechnology resources grants and general clinical research center grants which have components relevant to arrhythmia. (See Section 1.1.M for general description of DRR activities.)

In FY 72, the DRR supported six biotechnology resources grants which had seven related research components (FY 72: $40,954--%) and 18 clinical center grants which had 25 related research components (FY 72: $379,938--%).

Included among the supported efforts are:

- Provision of computer support in the studies of arrhythmia such as studies of the electrophysiology of cardiac muscle, left ventricular end-diastole, stochastic point processes in physiology, systolic time intervals, EKG, effects of drugs on electrochemical coupling

- Clinical support for studies of antiarrhythmic compounds
- Clinical support for studies of heart functioning, hemodynamic and conduction characteristics
- Clinical support for studies on disturbances to heart rhythm due to medications for other diseases
- Clinical support for treatment of heart block by radiowave transmission.

1.10 CARDIAC FAILURE

1.10.A Cardiac Failure--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

1.10.B Cardiac Failure--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported research activities are related directly to this area.

1.10.C Cardiac Failure--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

1.10.D Cardiac Failure--National Institute of Dental Research

The NIDR funds and administers research related to this area. (See section on coronary heart disease, 1.3.D, for topic description.)

1.10.E Cardiac Failure--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

1.10.F Cardiac Failure--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

1.10.G Cardiac Failure--National Institute of General Medical Sciences

The Pharmacology-Toxicology Program, NIGMS, funds and administers a large center program* which has one portion of the integrated studies devoted to the potential use of dopamine in congestive heart failure and hypertension. Though of peripheral interest to the problem, the group is also investigating optimum drug therapy for the management of acute renal failure associated with hypotension or shock. Another group within this center is studying new drugs (e.g., clonidine, guancydine) which show some promise as antihypertensives. In addition, a study is being undertaken to determine whether commonly used drugs interfere with maintenance of digoxin drug levels in the blood of patients on digoxin therapy. These studies are part of a large program devoted to the study of the basic mechanism of the action of drugs.

1.10.H Cardiac Failure--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

* While total funding of this center grant was available, no dollar level was available for this portion of the center program.

1.10.I Cardiac Failure--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

1.10.J Cardiac Failure--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L.480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

1.10.K Cardiac Failure--Bureau of Health Manpower Education

In FY 72, the BHME, Division of Nursing, funded and administered one research grant relevant to cardiac failure.

- Hospital Teaching of Patients with Heart Failure. The study is to determine if an intensive in-hospital teaching program for patients with congestive heart failure increases adherence to the discharge medical regime and reduces the number and length of subsequent hospitalizations.

  Selected patients with congestive heart failure admitted to two medical floors of the Columbia-Presbyterian Medical Center will be placed in either a control or study group. Following admission, all patients will be interviewed to determine

daily life patterns and understanding of congestive heart failure and project discharge medical regime.

During hospitalization a professional nurse will instruct study patients and then significant others regarding basic anatomy and physiology, pathology, diet, medications, rest and activity, predisposing factors, signs of impending failure and importance of continual follow-up. Teaching will be conducted individually and in groups using prepared audiovisual aids. After discharge all patients in control and study groups will be followed and an evaluation made (FY 72: $16,778).

For description of additional related manpower activities supported by BHME, Division of Allied Health, see Section 1.2.K.

1.10.L Cardiac Failure--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases.
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research

1.10.M Cardiac Failure--Division of Research Resources

In FY 72, the DRR supported 14 clinical center grants which had 14 related research components (FY 72: $222,326--%) including:

- Clinical support for studies on coronary insufficiency

- Clinical support for studies on the effects of cardiac glycosides and other cardiovascular agents
- Clinical support for studies on valvular incompetence
- Clinical support for studies on computer diagnostic techniques
- Clinical support for studies on action of diuretics in congestive heart failure
- Clinical support for studies on cardiac function with permanent pacemakers.

See Section 1.1.M for general description of DRR activities.

1.11 SHOCK

1.11.A Shock--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

1.11.B Shock--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported research activities are related directly to this area.

1.11.C Shock--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

1.11.D Shock--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

1.11.E Shock--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

1.11.F Shock--National Eye Institute

The NEI funds and administers research related to this area:

- Experimental Fluorescein Angiography (FY 72: $49,906). This research project includes a study of hypovolemic shock and its effect on intraocular tissues, choroidal and retinal blood flow; and blood gas changes and their effect on retinal vessels. The overall project goal is to achieve a reliable method of estimating change in relative retinal blood flow

- Ultrastructural Study of Ocular Vascular Permeability. (See Section 1.1.F for description of this project.)

- Retinal Circulation Times. (See Section 1.5.F for description of this project.)

- System Development to Study Ocular Vascular Dynamics. (See Section 1.1.F for description of this project.)

- Development of Noninvasive Techniques for Estimating Retinal and Choroidal Blood Flow. (See Section 1.1.F for description of project.)

1.11.G Shock--National Institute of General Medical Sciences

The Trauma Research Program, NIGMS, funds and administers a program related to this area (FY 72: eight center grants and 30 project grants).

The centers perform multidisciplinary research on total body response to severe trauma. This program involves many of the task groups included in the four categories of the NHLI organization, but only as they relate to a better understanding and care of the critically injured. A good example is shock. All severe multiple injuries are associated with hypovolemic

shock, a condition which must be reversed for survival. In the research performed with the NIGMS trauma grants, the development of more rapid measures for reversing shock must accompany studies of the underlying pathology of sequential organ failure and cellular damage. Resuscitative measures such as restoring adequate circulation, respiration and body metabolism provide the source material for the primary investigations. Cardiac, pulmonary and renal failures in injured patients present such unique pathology as posttraumatic pulmonary insufficiency, myocardial depressant activity, and profound circulatory defects following burn injury. Microcirculatory thrombosis associated with platelet abnormalities are major unsolved problems of the multiple injured patient. Research in the broadest sense is being performed to provide a better understanding of all aspects of severe trauma.

Among these NIGMS supported studies are:

- An Investigation of the Traumatized Patient (FY 72: $47,492--8). This program project includes among its studies investigations of:
  - Changes in fluid and electrolytes in response to hemorrhagic, septic and other forms of shock
  - Changes in blood viscosity in relation to burn and hemorrhagic shock
  - Definition of the low flow state
  - Changes in energy requirements in relation to trauma beyond that produced by starvation alone
  - The effects of various types of shock upon pulmonary hemodynamics and respiratory function
  - Evaluation of a circulatory assist device unit.

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- An On-line Computer Study of Therapy for Human Shock (FY 72: $216,645). This project is designed to investigate the disturbed physiology which results in post-traumatic acute respiratory distress syndrome. Techniques of mathematical modeling, computer simulation, and pattern recognition are used to derive numerical data concerning the gas-liquid interface and of the ventilation perfusion abnormalities within the lung.

- A Study of Intravascular Coagulation and Morbidity Following Trauma (FY 72: $16,124--%). Among the goals of this project are:

  - To investigate factors which affect healing of tissues following trauma to determine means to accurately assess healing

  - To study problems of oxygen transport in the trauma patient.

- An Evaluation of Saline Solutions in the Therapy of Shock (FY 72: $73,123).

- A Study of Clinical and Experimental Shock (FY 72: $28,580--%). Among the goals of this project are:

  - To obtain hemodynamic and metabolic data from patients in shock, especially those with cardiac disorders or with extensive inflammation

  - To determine the effects of prophylactic use of a mono-amine oxidase inhibitor, iproniazid inflammation

  - To determine the influence of hematocrit on continuing hemorrhage--studying cardiac output, blood viscosity and clotting factors and bleeding rate in dogs with normal and low hematocrits.

I.11.H Shock--National Institute of Child Health and Human Development

In FY 72, the NICHD funded and administered two research grants related to shock (FY 72: $52,229).

- Shock in Infancy--Metabolic and Hemodynamic Aspects. The major objectives of this investigation are to determine the physiologic and pathophysiologic responses made by the neonate subjected to a life-threatening challenge. An animal preparation is used in order to obtain hemodynamic and metabolic information under controlled conditions and to provide a means of refining and developing techniques for safe hemodynamic measurements on small subjects. The specific aims are to investigate the role metabolic acidosis plays in neonatal hemorrhagic shock, the significance of the elevated arterial oxygen tension that develops following hemorrhage, and to develop a clinical technique for the measurement of cardiac output in tiny subjects. (FY 72: $30,430).

- Role of Hageman Factor on Neonatal Disease. The specific aims of this project are:

  - To determine the role of Hageman Factor in the pathophysiologic changes in newborns with gram-negative septicemia

  - To study the change in Hageman Factor in young and adult rabbits given endotoxin and the effect of Factor XII inhibitors in these reactions

  - To determine the level of Hageman Factor inactivation necessary to protect rabbits from the generalized Shwartzman reaction. These studies are directed, in part, at elucidating the observation that newborn infants with a high incidence of gram-negative infections have a disproportionately low incidence of accompanying endotoxic shock (FY 72: $21,799).

1.11.I Shock--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

1.11.J Shock--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program) Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

1.11.K Shock--Bureau of Health Manpower Education

For description of related manpower activities supported by BHME, Division of Allied Health Manpower, see Section 1.2.K.

1.11.L Shock--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases

- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

1.11.M Shock--Division of Research Resources

In FY 72, DRR supported one clinical center grant which had a research component (FY 72: $34,470--%) related to shock. This research component was concerned with the provision of clinical support for the study of oxygen utilization in shock.

II. LUNG DISEASES

II. LUNG DISEASES

This section summarizes research activities (exclusive of intramural programs) supported in fiscal year 1972 (FY 72) by organizational components of the National Institutes of Health, exclusive of the National Heart and Lung Institute, in 14 categories:

- The Normal Lung (Section 2.1)
- Environmental Respiratory Diseases (Section 2.2)
- Emphysema and Chronic Bronchitis (Section 2.3)
- Pediatric Obstructive Respiratory Diseases (Section 2.4)
- Allergic Airway Diseases--Asthma (Section 2.5)
- Diffuse Interstitial Respiratory Diseases (Section 2.6)
- Infectious Respiratory Diseases (Section 2.7)
- Sarcoid and Granulomatous Lung Diseases (Section 2.8)
- Hypersensitivity Lung Diseases (Section 2.9)

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- Pulmonary Vascular Disease (Section 2.10)
- Hyaline Membrane Disease of the Newborn (Section 2.11)
- Cystic Fibrosis (Section 2.12)
- Acute and Chronic Respiratory Failure (Section 2.13)
- Extrapulmonary Manifestations of Respiratory Diseases (Section 2.14).

2.1 THE NORMAL LUNG

2.1.A The Normal Lung--National Institute of Allergy and Infectious Diseases

During 1972, NIAID awarded one grant related to this area ($30,268). This supports a detailed electron microscopy study of the structural and functional changes taking place in cells--such as the macrophages--entering the alveoli following injections of rabbits with microorganisms (BCG). An effort is being made to characterize electron-dense structures observed in alveolar macrophages so that their role in the immune response can be determined.

2.1.B The Normal Lung--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area (FY 72: one grant, totalling $25,380--%).

- A study of Mitochondrial Metabolism. As part of this study, mitochondrial function as it relates to intermediary metabolism of long-chain free fatty acids and the effects of guanidine derivatives on mitochondrial function are being investigated. Studies have included exploration of the substrate and end product specificity of guanidine compound-induced respiratory inhibition, and the mechanism of accumulation of guanidine compounds within mitochondria and its relationship to respiratory inhibition.

2.1.C The Normal Lung--National Cancer Institute

The NCI funds and administers one program project grant with a component relevant to the normal lung. It is a study

entitled Effect of Irradiation on the Lungs (FY 72: $25,727--%). (No detailed description of this project was available at the time this report was prepared.)

2.1.D The Normal Lung--National Institute of Dental Research

The NIDR funds and administers research related to this area (FY 72: 28 grants, totalling $1,096,695).

This grant supported research is focused on collagen and elastin--which is fundamental to an understanding of oral--or lung tissues in the healthy and diseased state. Among these studies are investigations of:

- Characterization of the microfibrils of connective tissue
- Control of collagen synthesis and degradation
- Collagen synthesis and extrusion by fibroblasts in culture
- Conjugated proteins in connective tissue
- Molecular packing of collagen in mineralized and nonmineralized tissues
- Normal and transformed fibroblast cells.

2.1.E The Normal Lung--National Institute of Environmental Health Sciences

The NIEHS funded and administered, in FY 72, a program project entitled Pulmonary Effects of Environmental Oxidant Pollutants.

Rats and nonhuman primates are exposed to oxidant air pollutants of a photochemical type, primarily oxone and nitrogen dioxide, at concentrations approximating high ambient levels. Structural-functional correlates of the effects will be assessed by integrated physiologic, morphometric and biochemical studies. Specific pathogenetic relationships to be sought, by determination of appropriate parameters, are: 1) between changes in pulmonary function and morphometry of airways, alveoli and the blood-air barrier; 2) between decreased resistance to infection and enzymatic defects and lipid peroxidation in pulmonary alveolar macrophages; 3) between morphometry of the blood-air pathway and lipid peroxidation. Other hypotheses to be tested concern the concept of oxidant lung damage as an acceleration of lipid peroxidation--molecular damage and the possible prophylactic effect of diets with increased content of vitamin E and other antioxidants.

Two research components of this program project entitled:

- Morphology of lungs exposed to oxidant pollutants
- Physiology of lungs exposed to oxidant pollutants

are related to the effects on the normal lung (FY 72: $186,826--%).

In addition, NIEHS funded and administered four research grants ($223,473) related to the impact of environmental agents on the lung. These were:

- Absorption of pollutants in the respiratory tract
- Ultrastructural alterations of NO_2-exposed lungs
- Response of alveolar macrophages to inhaled particles
- Alteration of NO_2 or NO_3 toxicity in lungs by vitamin E.

2.1.F The Normal Lung--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.1.G The Normal Lung--National Institute of General Medical Sciences

The Diagnostic Radiology Program, NIGMS, funds and administers projects for the development and application of new knowledge and techniques for the improved diagnosis of disease using ionizing and infrared radiation, radioisotopes and ultrasound.

Investigations have led to the development of new techniques for using radioisotopes and computer controlled radioactivity detectors to evaluate lung function.

2.1.H The Normal Lung--National Institute of Child Health and Human Development

The NICHD funds and administers eight research grants in the area of the normal lung.

- Lung Growth (FY 72: $13,551). The study objective is to ascertain the mode of development of the respiratory tissue in the human lung by utilizing a technique that has long been discarded as being too difficult to apply to lung tissue--namely, the reconstruction of wax models from serial sections of lungs ranging in age from the 30th week of fetal life to early childhood.

  To this technique there has now been added a new one--namely, the drawing of serial sections on transparent plastic plates and studying them in stacks of ten or more. For the first time, it is possible to effectively look inside the lung.

- Lung Maturation, Hormonal and Other Influences (FY 72: $39,308). The overall objective of this research project is to study various endocrine influences on the maturation of the fetal lung with particular attention to surfactant. The long-term goal is the development of means for the prophylaxis of hyaline membrane disease. Structural and biochemical parameters of lung maturation are to be determined in a series of animal endocrine deficiency and substitution experiments. The human disorders, anencephaly and antenatal bacterial amniotic fluid infection syndrome will also be examined for adrenal and pulmonary parameters of maturation.

- Functional Aspects of Pulmonary Immaturity. The purpose of the study is to define in physiologic terms the limits of pulmonary function in the small premature. Application of this knowledge to the clinical problem of respiratory insufficiency will suggest new therapeutic maneuvers anticipated to improve mortality and reduce physical and mental morbidity in this high risk group.

  This project is identifying specific abnormalities in lung function, as preliminary observations suggest that they are extensive. Studies are being carried out to attempt to improve pulmonary function by increasing lung volume.

- Lung Lecithin Synthesis--Normal and Asphyxial (FY 72: $78,564). The lung is dependent upon a surfactant or antiatelectasis factor to neutralize surface tension within the alveolus and permit it to remain open at low transpulmonary pressures. The functional portion of surfactant is thought to be a unique species of lecithin (phosphatidyl choline) with saturated long-chain fatty acids at both the C-1 and C-2 positions. This research application is designed to investigate the synthesis of disaturated phosphatidyl choline in the mature and fetal mammalian lung and is relevant to an understanding of the maturation of surfactant production in the mammalian fetus, the susceptibility of this mechanism to such insults as asphyxia and the etiologic importance of such insults in the genesis of respiratory distress in newborns.

- Biosynthesis of Pulmonary Active Lipids (FY 72: $30,587). The available pathways for synthesis of disaturated surface-active lecithin in the lung are studied. The work isolates and identifies the lipid methyltransferase enzymes of lung and studies the relative rates of surfactant biosynthesis of this and other enzyme pathways. The methods of study involve standard enzyme isolation and kinetic techniques. In vivo studies are being carried out in the adult dog following unilateral pulmonary artery ligation and in the fetal lamb in varying stages of gestational maturity.

- Biochemical Development of Surface Activity of Lung (FY 72: $46,804). These are studies of the pathways in the biosynthesis of lecithin (and other phospholipids) in the developing mammalian fetal lung, particularly in human. They are designed to quantify the products, to establish the fatty acids and their esterified positions on the molecule and to study the effects of abnormal physiological states on production of the phospholipids. Hyaline membrane disease in the human is studied as an example of a human problem in development associated with alterations in phospholipid metabolism. The same techniques are also being used to study oxygen toxicity and effects of administered anesthetic agents as examples of iatrogenically induced abnormal physiologic states.

- Fetal Oxygenation (FY 72: $35,827). The objective of these studies is to answer the following questions:

  - To what extent do changes in umbilical blood flow affect fetal acid-base balance?

  - To what extent do changes in maternal and/or fetal acid-base balance affect uterine and/or umbilical blood flow?

  - To what extent do the changes in fetal acid-base balance affect the fetal heart rate?

  - To what extent can the developing fetus use his renal system in the correction of chronic changes in acid-balance?

  - To what extent does loss of placental surface affect fetal oxygenation?

  - To what factors are fetal blood properties with respect to oxygen carriage attributable (FY 72: $35,827)?

- Ultrastructural Studies of the Lung (FY 72: $41,437). The purpose of this study is to obtain information concerning the uptake, intracellular transport and excretion of palmitic-9, 10H3 acid in normal adult and fetal rabbits and to compare these findings with those of the study of immature rabbits with the equivalent of respiratory distress syndrome.

In addition, the NICHD funds and administers three program project grants with components relevant to the normal lung:

- Pulmonary Ultrastructural Studies (FY 72: $29,461--%). A study to better understand the basic mechanism of fetal development as examined in cats, rats and the human.

- Clearance of Pulmonary Fluid at the Time of Birth (FY 72: $2,904--%). A study of the mechanism responsible for the clearance process.

- Cardiopulmonary Adaptation to Birth (FY 72: $19,032--%). A study of the adaptation process in sheep.

NHLI

2.1.I The Normal Lung--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.1.J The Normal Lung--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

2.1.K The Normal Lung--Bureau of Health Manpower Education

No identified ongoing BHME supported activities are related directly to this area.

2.1.L The Normal Lung--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases

- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.1.M The Normal Lung--Division of Research Resources

The Division of Research Resources (DRR) provides support for noncategorical resources to biomedical research institutions in support of categorical research activities of NIH. DRR supports programs in four basic areas:

- General Clinical Research Centers Program. This program supports discrete clinical units (usually in university or university affiliated hospitals), which are utilized in the conduct of multicategorical clinical research

- Biotechnology Resources Program. This program supports the development and operation of large and complex technological resources (e.g., computer systems, electron microscopy service laboratories, mass spectrometry and nuclear magnetic resonance systems) for their application to biomedical research problems

- Animal Resources Program. This program provides support for the development and improvement of various animal models, including nonhuman primates, for use in biomedical research as well as the upgrading of institutional animal resources

- General Research Support Program. This program provides general research support to health professional and university graduate schools and other biomedical research organizations. (This program, in FY 72, derived its funds from separate appropriations to the National Institutes of Health and the National Institute of Mental Health; however, it was administered by DRR.)

* DRR funds resources which contributed to performance of studies documented in each DRR section.

In FY 72, the DRR supported six biotechnology resources grants with 14 components (FY 72: $184,000--%) related to studies of the normal lung.

These studies included:

- Spatial Distribution of Pulmonary Ventilation (in dogs and chimpanzees)
- Spatial Distribution of Lung Parenchyma
- Pressure Volume Diagrams of the Lungs and the Air-Flow Distribution Function
- Effects of Breathing Liquid Fluorocarbons in Regional Imbalances (in dogs)
- Lung Volume Data and Pulmonary Function Tests
- Automatic Respiratory Calibration
- Spirometry for Pulmonary Function Testing (human)
- Functional Residual Capacity of the Lungs (human).

In FY 72, the DRR supported four general clinical center grants with four relevant components (FY 72: $64,600--%). These studies included:

- Breathing and Ventilation Response to Oxygen and Carbon Dioxide (human)
- Pulmonary Physiology in Infants and Children
- Pulmonary Compliance in Infants
- Secretion and Removal of Pulmonary Surfactant in Alveolar Proteinosis (human).

2.2 ENVIRONMENTAL RESPIRATORY DISEASES

2.2.A Environmental Respiratory Diseases--National Institute of Allergy and Infectious Diseases

A single NIAID award (FY 72: $43,577) supports an immunologic study of hypersensitivity pneumonitis. The production of local "secretory" antibody in allergic and nonallergic individuals, following exposure to ragweed and other antigens, is being compared. An attempt is being made to develop the rat and/or guinea pig as an experimental animal model for the study of hypersensitivity pneumonitis.

2.2.B Environmental Respiratory Diseases--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported activities are related directly to this area.

2.2.C Environmental Respiratory Diseases--National Cancer Institute

For description of related research activities supported by NCI, see Section 2.14.H.

2.2.D Environmental Respiratory Diseases--National Institute of Dental Research

No identified ongoing NIDR supported activities are related directly to this area.

2.2.E Environment Respiratory Diseases--National Institute of Environmental Health Sciences

NIEHS funds and administers four program projects with primary direct relationship to environmental lung diseases (FY 72: five project components funded at $765,735--%). These are:

- Center for Study of The Human Environment. The Center for the Study of the Human Environment is devoted to the study of environmental problems which affect man's health and to research training in pertinent scientific disciplines. The present subject areas on which coordinated research efforts are focused include pulmonary problems of environmental origin. The environmental origins of these problems are related to air and water quality, solid waste management, industrial and agricultural activity, and consumer products including food, drugs, household and other manufactured materials.

- Respiratory Disease and Aerosol Physiology. A component of a program project entitled "Research in the Environmental Health Sciences." This project is directed at determining the effects of aerosols on patients with pneumoconiosis, chronic bronchitis and emphysema.

- Asbestos Exposure-Risk in Defined Human Populations. Various population groups with differing levels of asbestos exposure over a period of 20 or more years are being investigated to determine the level of asbestos exposure dangerous to health.

- A Program in Environmental Physiology and Toxicology. This program has two related components entitled "Effects of low level CO exposure on circulation" and "Effects of dehydration and temperature." In the former, carbon monoxide is being studied with epidemiological, behavioral, biochemical and physiological techniques. Blood from people dying suddenly is studied and CO levels related to the cause of death. The possibility of 2,3 DPG in red blood cells as an adaptive mechanism to CO exposure will be evaluated. Behavioral changes related to tissue hypoxia from CO

will be compared to similar O_2 levels resulting from hypoxic hypoxia. Effects of CO on the coronary circulation, on cardiovascular changes at the onset of exercise and on the distribution of blood flow throughout the body is being studied.

In the latter study, the role of dehydration and temperature on susceptibility to environmental agents and the mechanisms underlying these effects is being studied. Mucociliary clearance and particle deposition under various climatic conditions will be continued. The biological and toxicological effects of phthalate ester plasticizers and organic solvents, the effects of environmental stress on the cholinergic nervous system and the effects of trace metals on the nervous system will be studied. The effects of various toxins on the facilitated transport of O_2 and CO will be related to other physiologic effects. UV air disinfection will be tested for its effectiveness in limiting airborne infection in hospitals.

In addition, NIEHS funded and administered four research grants (FY 72 funding: $198,830) related to environmental respiratory diseases:

- Pathogenesis of Pulmonary Berylliosis. Deposition and clearance levels of beryllium in the lungs of the several animals is being studied. This research is expected to clarify the nature of the immunologic component in the etiology of pulmonary berylliosis, and to suggest means by which the development of this disease could be inhibited.

- Upper Respiratory Tract Clearance. The objectives of this research project are to characterize clearance parameters under normal conditions and under various conditions of stress (dusts, noxious gases, bacteria and metabolic stimuli) to the pulmonary system to achieve an understanding of the basic physiological and homeostatic mechanisms which apply in mammals to the clearance of particulates from the lungs--and to utilize this information in the realistic appraisal of the hazard associated with the inhalation of respirable dusts and air pollutants in man.

- Inhalation Toxicology of Environmental Agents. The broad objective of this proposal is the continued development of a program in inhalation or pulmonary toxicology. It is intended to apply to selected substances and to realistic mixtures a methodological approach designed to provide sufficient and appropriate data on the pharamcokinetic constants of an inhaled atmosphere to permit a degree of prediction of the disposition of an inhaled dose, an estimate of probable toxicity and a reasonable basis for investigation of the mechanisms of toxic effects.

- Automobile Exhaust and Chronic Respiratory Disease. This study is designed to follow a selected segment of the population over an extended period of time and record the rate of change of signs and symptoms associated with the development of chronic respiratory disease. Intense exposure to automobile exhaust and cigarette smoking are the major environmental agents to be evaluated. The assessment of the population includes interview by standard questionnaires, measurements of ventilatory capacity, evaluation of sputum production, both qualitatively from a bacteriological standpoint and quantitatively in amount, and an evaluation of the host response mechanisms by relatively detailed immunological analyses. Exposure to the environment is assessed by several techniques. These include environmental sampling as measured by standard monitoring equipment and personal sampling devices. In addition, measures of biologically incorporated constituents of automobile exhaust, particularly carbon monoxide and lead, are being determined. By studying prospectively a relatively healthy segment of the population, it is believed that factors related to susceptibility to chronic respiratory diseases in high-risk individuals can be identified.

2.2.F Environmental Respiratory Diseases--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.2.G Environmental Respiratory Diseases--National Institute of General Medical Sciences

No identified ongoing NIGMS supported research activities are related directly to this area.

2.2.H Environmental Respiratory Diseases--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

2.2.I Environmental Respiratory Diseases--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.2.J Environmental Respiratory Diseases--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.)

2.2.K Environmental Respiratory Diseases--Bureau of Health Manpower Education

For description of related manpower activities supported by BHME, see Section 2.3.K.

2.2.L Environmental Respiratory Diseases--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

An example of an NLM sponsored activity categorically related to this area is a P.L. 480 supported project entitled Critical Review: Pneumoconiosus in Coal Miners.

2.2.M Environmental Respiratory Diseases--Division of Research Resources

In FY 72, DRR supported one general clinical research center which had a relevant research component entitled, Diagnosis and Therapy of Industrial Lung Diseases (FY 72: $31,951--%).

See Section 2.1.M for general description of DRR activities.

2.3 EMPHYSEMA AND CHRONIC BRONCHITIS

2.3.A Emphysema and Chronic Bronchitis--National Institute of Allergy and Infectious Diseases

Three NIAID grants, totalling $175,388, support studies in this area. Of special interest are the occurrence of and immune response to viral and bacterial infections in persons with chronic bronchitis and emphysema. Also under study is the effect of the organism Mycoplasma pneumoniae (a cause of pulmonary disease in humans) on the bronchial tissue of hamsters.

2.3.B Emphysema and Chronic Bronchitis--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported activities are related directly to this area.

2.3.C Emphysema and Chronic Bronchitis--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

2.3.D Emphysema and Chronic Bronchitis--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

2.3.E Emphysema and Chronic Bronchitis--National Institute of Environmental Health Sciences

For description of related research activities supported by NIEHS, see Sections 1.1.E and 2.2.E.

2.3.F Emphysema and Chronic Bronchitis--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.3.G Emphysema and Chronic Bronchitis--National Institute of General Medical Sciences

The NIGMS funds and administers research in this area. In FY 72, this consisted of a Study on the Pathology of the Lung (FY 72: one grant, totalling $9,795--%).

The objective of the NIGMS sponsored program in experimental pathology is to assist in the elucidation of the etiology and pathogenesis of certain diseases in man. This study of the pathology of the lung deals with the effects of lathyrogenic agents and nitrogen dioxide on the trachea and lung in chronic bronchitis and emphysema.

2.3.H Emphysema and Chronic Bronchitis--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

2.3.I Emphysema and Chronic Bronchitis--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.3.J Emphysema and Chronic Bronchitis--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480 --Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

2.3.K Emphysema and Chronic Bronchitis--Bureau of Health Manpower Education

The Division of Allied Health Manpower funds and administers training programs related to this area (FY 72: 15 grants, totalling $545,985). These are traditional training programs for the preparation of respiratory (inhalation) therapists.

Among the therapist's responsibilities are the performance of the following: 1) administration of gas, humidity and aerosol therapy; 2) administration of intermittent positive pressure breaking treatment; 3) assistance with long-term continuous artificial ventilation, 4) performance of special procedures of cardiopulmonary resuscitation; 5) administration

of drugs through inhalation procedures; 6) performance of tasks related to patient care (especially those of airway management and respiratory therapy). In addition the therapist must have degree of knowledge of anatomy, physiology, pharmacology, and clinical medicine.

2.3.L Emphysema and Chronic Bronchitis--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.3.M Emphysema and Chronic Bronchitis--Division of Research Resources

In FY 72, the DRR supported 10 general clinical center grants with 12 relevant components (FY 72: $167,541--%). These studies included:

- Pulmonary Emphysema with Alpha-Antitrypsin Deficiency (human)
- Chronic Obstructive Pulmonary Disease (human)
- Role of Infection in Emphysema (human)
- Hypercapnic States in Chronic Pulmonary Disease (human)

- Infection and Immunity in Chronic Bronchitis (human)
- Chemotherapy in Treatment of Chronic Bronchitis (human)
- Therapy in Chronic Obstructive Pulmonary Diseases (human)
- Effect of Oxygen on Pulmonary Circulation in Man
- Left Ventricle Function in Chronic Lung Disease (human).

For general description of DRR activities, see Section .1.M.

2.4 PEDIATRIC OBSTRUCTIVE RESPIRATORY DISEASES

2.4.A Pediatric Obstructive Respiratory Diseases--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported activities are related directly to this area.

2.4.B Pediatric Obstructive Respiratory Diseases--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported activities are related directly to this area.

2.4.C Pediatric Obstructive Respiratory Diseases--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

2.4.D Pediatric Obstructive Respiratory Diseases--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

2.4.E Pediatric Obstructive Respiratory Diseases--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

2.4.F Pediatric Obstructive Respiratory Diseases--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.4.G Pediatric Obstructive Respiratory Diseases--National Institute of General Medicine Sciences

No identified ongoing NIGMS supported research activities are related directly to this area.

2.4.H Pediatric Obstructive Respiratory Diseases--National Institute of Child Health and Human Development

NICHD sponsored one research grant related to this area.

- Respiratory Studies in Infants and Young Children (FY 72: $51,195). This research aims to:
  - Develop methods for studying respiratory mechanics in infants
  - Measure the effects of bronchiolitis and its therapy on respiratory mechanics
  - Accumulate longitudinal data on development of normal respiratory mechanics in the growing child.

2.4.I Pediatric Obstructive Respiratory Diseases--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.4.J Pediatric Obstructive Respiratory Diseases--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

2.4.K Pediatric Obstructive Respiratory Diseases--Bureau of Health Manpower Education

BHME supported activities related directly to this area are described in Section 2.3.K.

2.4.L Pediatric Obstructive Respiratory Diseases--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.4.M Pediatric Obstructive Respiratory Diseases--Division of Research Resources

In FY 72, the DRR supported one biotechnology resources grant with two relevant components (FY 72: $39,654--%). These studies addressed:

- Regional distribution of ventilation and pulmonary blood flow (human)
- Acute ventilatory insufficiency (human).

Additionally, DRR supported one general clinical center grant with a relevant component (FY 72: $8,045--%) which addressed:

- Tracheo-bronchiomegaly (human).

For description of DRR classes of activities, see Section 2.1.M.

2.5 ALLERGIC AIRWAY DISEASES--ASTHMA

2.5.A Allergic Airway Diseases--Asthma--National Institute of Allergy and Infectious Diseases

Twelve NIAID grants support studies of asthma (FY 72: $675,437). Six of these awards established Asthma and Allergic Disease Centers in institutions where laboratory and clinical studies of asthma are closely interwoven. Investigations at these Centers include studies of the role of cyclic AMP in the development of bronchial asthma, viral respiratory infections and bronchial asthma in children, bacterial nonpathogens and asthma, and methods of classifying, diagnosing, and treating various clinical forms of the disease.

Other asthma research projects supported by NIAID are focused on aspirin sensitivity in asthmatics, development of animal models for the study of asthma, and evaluation of the theory that asthma is the result of defective functioning of beta adrenergic mechanisms (a part of the nervous system) in bronchial tissues of allergic individuals.

2.5.B Allergic Airway Diseases--Asthma--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported activities are related directly to this area.

2.5.C Allergic Airway Diseases--Asthma--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

2.5.D Allergic Airway Diseases--Asthma--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

2.5.E Allergic Airway Diseases--Asthma--National Institute of Environmental Health Sciences

NIEHS funds and administers (FY 72: $44,372--%) one project entitled "Lung Center" related to asthma. This project is a component of a program project entitled "Environmental Physiology and Toxicology" which is described in Section 2.2.E.

2.5.F Allergic Airway Diseases--Asthma--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.5.G Allergic Airway Diseases--Asthma--National Institute of General Medical Sciences

No identified ongoing NIGMS supported research activities are related directly to this area.

2.5.H Allergic Airway Diseases--Asthma--National Institute of Child Health and Human Development

NICHD supports one research grant related to this area:

- Infection and Childhood Obstructive Airway Disease (FY 72: $52,520). This research concerns the role of viral respiratory diseases in the production and exacerbation of asthma. Viral cultures, antibody studies, trial vaccination and studies of familial atopy are planned in a large group of asthmatic children.

2.5.I Allergic Airway Diseases--Asthma--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.5.J Allergic Airway Diseases--Asthma--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

2.5.K Allergic Airway Diseases--Asthma--Bureau of Health Manpower Education

For description of related activities supported by BHME, see Section 2.3.K.

2.5.L Allergic Airway Diseases--Asthma--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.5.M Allergic Airway Disease--Asthma--Division of Research Resources

The DRR funds and administers a biotechnology resources grant and general clinical center grants relevant to allergic airway disease--asthma.

In FY 72, the DRR supported one biotechnology resources grant with a relevant component (FY 72: $4,173--%). This study addressed:

- Graduate Training in Air Pollution Control.

In FY 72, the DRR supported 9 general clinical center grants with 10 relevant components (FY 72: $142,047--%). These studies included:

- Gamma Globulin Metabolism in Man
- Inhalation Bronchial Challenge in Asthma
- Chemotherapy in Asthma
- Chemotherapy in Delayed Hyposensitivity Reactions in Children
- Allergic Disorders
- Cyclic Changes in Clinical Status of Menstruating Asthmatics
- Mechanism of Exercise-Induced Bronchoconstriction
- Treatment of Asthma Through Operant Conditioning

De[illegible]lopment of Childhood Eczema and Asthma.

See Section 2.1.M for a general description of DRR activities.

2.6 DIFFUSE INTERSTITIAL RESPIRATORY DISEASES

2.6.A Diffuse Interstitial Respiratory Diseases--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported activities are related directly to this area.

2.6.B Diffuse Interstitial Respiratory Diseases--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported activities are related directly to this area.

2.6.C Diffuse Interstitial Respiratory Diseases--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

2.6.D Diffuse Interstitial Respiratory Diseases--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

2.6.E Diffuse Interstitial Respiratory Diseases--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

2.6.F Diffuse Interstitial Respiratory Diseases--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.6.G Diffuse Interstitial Respiratory Diseases--National Institute of General Medical Sciences

No identified ongoing NIGMS supported research activities are related directly to this area.

2.6.H Diffuse Interstitial Respiratory Diseases--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

2.6.I Diffuse Interstitial Respiratory Diseases--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.6.J Diffuse Interstitial Respiratory Diseases--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

2.6.K Diffuse Interstitial Respiratory Diseases--Bureau of Health Manpower Education

BHME supported activities related directly to this area are described in Section 2.3.K.

2.6.L Diffuse Interstitial Respiratory Diseases--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.6.M Diffuse Interstitial Respiratory Diseases--Division of Research Resources

No identified ongoing DRR supported research activities are related directly to this area.

2.7 INFECTIOUS RESPIRATORY DISEASES

2.7.A Infectious Respiratory Diseases--National Institute of Allergy and Infectious Diseases

Six contracts and seven grants were awarded by NIAID in 1972 for studies of infectious respiratory diseases. The contracts, totalling $417,377, were mainly for the evaluation of experimental vaccines and for study of the prevalence of specific respiratory pathogens in defined population groups.

The seven research grants awarded by NIAID amounted to $445,875. Three of the projects are specifically directed toward acquiring a better understanding of the immune mechanisms involved in the development of tuberculosis. By defining, principally, the nature of acquired immunity to tuberculosis in animals, the scientists hope to develop a better vaccine for tuberculosis than that presently employed.

Other NIAID research projects in this area are concerned with long-term study of host-defense mechanisms in the lung and with elucidation of the interaction of virus, host, and environment which results in severe respiratory infections in some individuals.

2.7.B Infectious Respiratory Diseases--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area (FY 72: one grant, totalling $120,041).

- A Study of Renal, Vascular, and Pulmonary Structure in Disease. This involves a study of radiation

penumonitis. To date, striking changes have been observed in the alveoli and the capillaries of rat lung given high doses (2000-5000 rads) of radiation. These consist of detachment of cells from the basement membrane and increase in amount of septal connective tissue. The progression and outcome of these changes are being studied by means of electron microscopy.

2.7.C Infectious Respiratory Diseases--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

2.7.D Infectious Respiratory Diseases--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

2.7.E Infectious Respiratory Diseases--National Institute of Environmental Health Sciences

NIEHS funds and administers a program project entitled "Pulmonary Effects of Environmental Oxidant Pollutants" (described in Section 2.1.E), a component of which "Oxidant Pollutants and Susceptibility to Viral Infections" is related to infectious respiratory diseases (FY 72: one project, $93,413--%).

2.7.F Infectious Respiratory Diseases--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.7.G Infectious Respiratory Diseases--National Institute of General Medical Sciences

No identified ongoing NIGMS supported research activities are related directly to this area.

2.7.H Infectious Respiratory Diseases--National Institute of Child Dealth and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

2.7.I Infectious Respiratory Diseases--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.7.J Infectious Respiratory Diseases--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program) Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

2.7.K Infectious Respiratory Diseases--Bureau of Health Manpower Education

BHME supported activities related directly to this area are described in Section 2.3.K.

2.7.L Infectious Respiratory Diseases--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.7.M Infectious Respiratory Diseases--Division of Research Resources

In FY 72, the DRR supported three general clinical center grants with three relevant components (FY 72: $46,494--%). These studies included:

- Chemotherapy of staphylococcal furunculosis and pneumonia (human)
- Lung lipids and alveolar macrophage function in cholesterol pneumonitis (human)
- Clinical findings in aspiration pneumonia in infants

For general description of DRR activities, see Section 2.1.M.

2.8. SARCOID AND GRANULOMATOUS LUNG DISEASES

2.8.A Sarcoid and Granulomatous Lung Diseases--National Institute of Allergy and Infectious Diseases

One NIAID award, in the amount of $30,428, was made in this area from FY 72 funds. Investigators are studying schistosomiasis, a serious parasitic disease, as a possible model of the characteristic formation in some chronic infections of granulomas (small nodules of tissue) in the lungs and other areas of the respiratory tract. These studies are also expected to increase scientific understanding of the interplay of immunological and biochemical factors in schistosomas disease.

2.8.B Sarcoid and Granulomatous Lung Diseases--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported activities are related directly to this area.

2.8.C Sarcoid and Granulomatous Lung Diseases--National Cancer Institute

For description of related research activities supported by NCI, see Section 2.14.C.

2.8.D Sarcoid and Granulomatous Lung Diseases--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

2.8.E Sarcoid and Granulomatous Lung Diseases--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

2.8.F Sarcoid and Granulomatous Lung Diseases--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.8.G Sarcoid and Granulomatous Lung Diseases--National Institute of General Medical Sciences

No identified ongoing NIGMS supported research activities are related directly to this area.

2.8.H Sarcoid and Granulomatous Lung Diseases--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

2.8.I Sarcoid and Granulomatous Lung Diseases--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.8.J Sarcoid and Granulomatous Lung Diseases--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

2.8.K Sarcoid and Granulomatous Lung Diseases--Bureau of Health Manpower Education

No identified ongoing BHME supported manpower activities are related directly to this area.

2.8.L Sarcoid and Granulomatous Lung Diseases--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.8.M Sarcoid and Granulomatous Lung Diseases--Division of Research Resources

In FY 72, the DRR supported one general clinical center grant with one relevant component (FY 72: $15,174--%). The study addressed:

- Effect of penicellamine on lung functions in pulmonary fibrosis (human).

For general description of DRR activities, see Section 2.1.M.

2.9 HYPERSENSITIVITY LUNG DISEASES

2.9.A Hypersensitivity Lung Diseases--National Institute of Allergy and Infectious Diseases

NIAID funds and administers research related to this area (FY 72: one contract, totalling $45,870; 14 grants, totalling $699,367).

The one contract supports the compilation of data on patient visits for allergic disease at two large health centers. This will provide much needed statistical information on the prevalence of allergies, particularly among persons in a rural environment.

The 14 grants awarded by NIAID in this area include two for support of Asthma and Allergic Disease Centers. At one of these emphasis will be on patients with allergic rhinitis; at the other, emphasis will be placed on improvement in diagnosing and treating patients with hay fever and other pollen allergies.

Many of the other NIAID grants support investigations of the various immunologic mechanisms involved in the production of allergic disease. One investigator is measuring immunologic changes that occur in ragweed sensitive patients as they undergo desensitization. A better understanding of the relationship between these changes and increased dose size is being sought. Other scientists are focusing on: 1) the beta-adrenergic blockade; 2) the cells producing antibody--particularly IgE and bronchial sensitivity; 3) the release of chemical mediators (such as histamine) from sensitized

monkey lung tissue; and 4) factors of host resistance in respiratory disease in children. The last-named study is a long-term investigation of new agents causing childhood respiratory illness and their evaluation as potential vaccine antigens. Transfer factor, a dialyzable substance obtained from sensitized lymphocytes, is also being analyzed biochemically and used as treatment for a number of diseases characterized by delayed hypersensitivity.

2.9.B Hypersensitivity Lung Diseases--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported research activities related directly to this area.

2.9.C Hypersensitivity Lung Diseases--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

2.9.D Hypersensitivity Lung Diseases--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

2.9.E Hypersensitivity Lung Diseases--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

2.9.F Hypersensitivity Lung Diseases--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.9.G Hypersensitivity Lung Diseases--National Institute of General Medical Sciences

No identified ongoing NIGMS supported research activities are related directly to this area.

2.9.H Hypersensitivity Lung Diseases--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

2.9.I Hypersensitivity Lung Diseases--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.9.J Hypersensitivity Lung Diseases--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note:

P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

2.9.K Hypersensitivity Lung Diseases--Bureau of Health Manpower Education

For description of related manpower activities supported by BHME, see Section 2.3.K.

2.9.L Hypersensitivity Lung Diseases--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.9.M Hypersensitivity Lung Diseases--Division of Research Resources

In FY 72, the DRR supported two general clinical center grants with two relevant components (FY 72: $19,679--%). These studies addressed:

- Pulmonary involvement in deficiencies of immune mechanisms (human)
- Evaluation of laminar air flow utilizing particle air filtration (human).

See Section 2.1.M for general description of DRR activities.

2.10 PULMONARY VASCULAR DISEASES

2.10.A Pulmonary Vascular Diseases--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

2.10.B Pulmonary Vascular Diseases--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported activities are related directly to this area.

2.10.C Pulmonary Vascular Diseases--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

2.10.D Pulmonary Vascular Diseases--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

2.10.E Pulmonary Vascular Diseases--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

2.10.F Pulmonary Vascular Diseases--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.10.G Pulmonary Vascular Diseases--National Institute of General Medical Sciences

The NIGMS funds and administers grant supported research related to this area.

Among these NIGMS supported studies are:

- An Investigation of the Traumatized Patient--Pulmonary Function. (See section on Shock for project description and FY 72 dollars for the total project.) This component of the project deals with the effects of various types of shock upon pulmonary hemodynamics and respiratory function.

- The Anesthesiology Program, NIGMS, funds and administers, as a major component, center and program project supported studies related to this area (FY 72: $4,300,000). A large part of these funds is spent in studies on the physiology of the normal lung, acute respiratory failure, pulmonary hypertension, and pulmonary edema to provide a better understanding of the reactions which occur before, during and after anesthetic induction. Anesthesiology has extended beyond the operating room to include resuscitation, respiratory emergencies, and inhalation therapy. The program includes investigations on pharmacology of anesthetics, obstetrical anesthesia, neonatal resuscitation, metabolic effects of anesthetics, the nature and control of pain, and anesthesia technology. An example of the resuscitative methods is the application of continuous positive pressure to the airway of infants with hyaline membrane disease by one of the investigators in the California program. This has led to reduction in the deaths of premature infants at this institution. Although the mechanisms of action are not

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fully understood, it is believed that the pressure applied enlarges the FRC allowing ventilation of small lung units until such time as the infant can maintain its own lung inflation.

2.10.H Pulmonary Vascular Diseases--National Institute of Child Health and Human Development

NICHD supports one research grant related to this area, entitled Lung-Hydraulic Impedance: Evaluation in Children (FY 72: $30,382). The aim of this research is to measure pulmonary vascular impedance in children with congenital heart disease in order to determine if this measurement is superior to that of pulmonary vascular resistance which is now commonly used.

2.10.I Pulmonary Vascular Diseases--National Institute of Neurological Diseases and Stroke

The Research Grants Branch, Extramural Programs, NINDS, funds and administers a grant supported center (FY 72: one grant, totalling $97,589*) which conducts studies in this area.

Pulmonary function studies conducted by this center are closely related with the center's cardiac function studies (see Heart and Blood Vessel Diseases, section on Arrhythmias). Pulmonary function studies are based on the hypotheses: 1) that the Cushing effect produces an increase in pulmonary

*This dollar total represents the amount of funding for the entire center grant, not only for the component pulmonary vascular disease studies.

vein pressure as a possible reversal precursor to pulmonary edema, 2) that catecholamine output may influence the precursor changes and be blocked pharmacologically, and 3) that central nervous system injury produces an incipient "physiologic" cardiac disease.

2.10.J Pulmonary Vascular Diseases--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

2.10.K Pulmonary Vascular Diseases--Bureau of Health Manpower Education

No identified ongoing BHME supported activities are related directly to this area.

2.10.L Pulmonary Vascular Diseases--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases

- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.10.M Pulmonary Vascular Diseases--Division of Research Resources

In FY 72, the DRR supported 9 general clinical center grants with 10 relevant components (FY 72: $135,058--%). These studies included:

- Inflammation-Related Coagulopathy in Chronic Lung Disease (human)
- Urokinase-Pulmonary Embolism Trial (human)
- Diurnal Variation in Arterial Blood Gases in Respiratory Failure (human)
- Control of Hypoxemia in Chronic Airway Obstruction (human)
- Coagulation in Primary Pulmonary Hypertension (human)
- Fatty Acid Toxicity (human)
- Operative Results of Mitral Valve Disease with Pulmonary Hypertension (human)
- Pulmonary Embolism (human)
- Pulmonary Hypertension in Children with Portal Hypertension

See Section 2.1.M for general description of DRR activities.

2.11 HYALINE MEMBRANE DISEASE OF THE NEWBORN

2.11.A Hyaline Membrane Disease of the Newborn--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

2.11.B Hyaline Membrane Disease of the Newborn--National Institute of Arthritis, Metabolism, and Digestive Diseases

NIAMDD funds and administers research related to this area (FY 72: one grant, totalling $23,316--%).

- A Study of Lipid Synthesis by the Rat Lung in Vitro. This study is part of a program project dealing with hormonal regulation of metabolism. (No further pertinent details were available.)

2.11.C Hyaline Membrane Disease of the Newborn--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

2.11.D Hyaline Membrane Disease of the Newborn--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

2.11.E Hyaline Membrane Disease of the Newborn--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

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2.11.F Hyaline Membrane Disease in the Newborn--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.11.G Hyaline Membrane Disease of the Newborn--National Institute of General Medical Sciences

The NIGMS Genetics Program funds and administers a project (FY 72: $15,000--%) in hyaline membrane disease as part of the NIGMS Genetics Center at the Mount Sinai School of Medicine, New York.

The objective of this project is to operationally define hyaline membrane disease by analysis of the phospholipid content of the trachea-esophageal mucus. This project involves a measurement of the lecithin/spingomyelin ratio of the phospholipid fraction as an indication of surfactant properties.

One additional related NIGMS supported study is described in Section 2.10.G.

2.11.H Hyaline Membrane Disease of the Newborn--National Institute of Child Health and Human Development

NICHD funds and administers research (FY 72: nine grants, totalling $410,514; one contract, totalling $21,100) related to hyaline membrane disease. These studies are:

- Biosynthesis of Pulmonary Surface Active Lipids (FY 72: $30,587). In a study of pulmonary surfactants, this research has indicated that the

primary compound is a dipalmitoyl phosphatidyl choline. The synthetic pathways involved and the timing and presence of precursors in lung tissue are being investigated. More extensive evaluation of lecithin is being done, including the effects of hypoxia, hyperoxia, acidosis, and various drugs on its biosynthesis.

- Ultrastructural Studies of the Lung (FY 72: $41,431). This research is concerned with the study of alveolar lining in pulmonary tissue of rabbits under a variety of conditions. The specific research plans include:

  - Study of fixation, preservation and high resolution characterization of alveolar lining layers

  - Autoradiographic and biochemical studies of lung lipids

  - Study of the transport of albumin using tritiated albumin.

  Investigation extends into the normal development of the alveolar lining layer of the fetal rabbit lung and the precursors of this lining in the respiratory distress syndrome of rabbit and human infants. Additional work includes the determination of the nature of inclusions in type II cells, lining layer and Clara cells of human RDS, and the study of the effects of asphyxia, hypoxia, acidosis and occlusion of the pulmonary artery and biochemical artery in immature rabbit lungs.

- Lung Edema, Immaturity and Hyaline Membrane Disease (FY 72: $76,596). This research assesses the role of pulmonary edema in the pathogenesis of hyaline membrane disease, and is based on observations that an increase in lung fluid is invariably associated with this disease at autopsy. To accomplish this purpose, measurements of hemodynamic pulmonary edema are being done in 1- to 3-day old pups *in vivo* and in isolated perfused lungs. This will allow a comparison of the effect of asphyxia on protein clearance and lung-water content in adult and newborn dogs. Additionally, the unilateral restriction of pulmonary blood flow from birth is being studied in lambs delivered prematurely.

- Phospholipid Metabolism During Development (FY 72: $19,490). The long-term goal of this research is to describe the developmental pattern and regulatory mechanisms in the biosynthesis of the phospholipid components of cellular membranes. The synthesis of lecithin, phosphatidyl ethanolamine, phosphatidyl serine and phosphatidyl inositol has been studied in tissue slices of lung and liver. Further studies include measurement of the incorporation of isotopic precursors into the individual phospholipid species and subspecies of intracellular organelles. The overall patterns of phospholipid synthesis derived from these studies are correlated with the activity of the individual enzymes in the biosynthetic pathways. All studies are repeated at various developmental phases.

- The Effect of Asphyxia on Fetal Lung Fluid (FY 72: $16,118). This project is studying the effects of intrauterine asphyxia on subsequent pulmonary function in the newborn lamb. Presumed pulmonary damage occurs during fetal asphyxia in sheep preparations. Various hemodynamic measurements are being taken in exteriorized fetal lambs with and without asphyxia, before and during positive pressure ventilation. These and other studies are aimed at demonstrating the presence of increased pulmonary capillary permeability in asphyxia.

- Biochemical Development of Surface Activity of the Lung (FY 72: $46,804). This project involves a detailed study of the biosynthesis and metabolism of lecithin in normal fetal and newborn lungs. A second aspect of the investigation is concerned with evaluating changes in lipid synthesis induced by acidosis, anoxia, hypercapnia, and hypothermia in fetal, newborn and adult sheep and monkeys. In-depth consideration of the enzymatic pathways for lung lecithin biosynthesis is being accomplished with particular reference to the effects of estrogenic metabolites and cyclic 3',5' - adenosine monophosphate.

- Lung Maturation, Hormonal and Other Influences (FY 72: $39,309). Study of the effects of various endocrine influences on the maturation of the fetal lung, and, in particular, the development of surfactant is the primary research aim of this project.

Additionally, anencephaly and antenatal bacterial amniotic fluid infections are being assessed in light of possible effects on adrenal and pulmonary maturation. These studies are aimed at more specific elucidation of clinical observations which have been made between adrenal size and the presence or absence of hyaline membrane disease in otherwise normal and in anencephalic neonates.

- Functional Aspects of Pulmonary Immaturity (FY 72: $61,656). The aim of this research is to define pulmonary function serially in a group of low birth weight infants and test methods which are designed to improve lung function of these infants. Four related projects are included:

  - Evaluation of constant negative pressure applied around the body of an infant to increase his functional residual capacity (FRC)

  - Further documentation of the changes in chest wall compliance and FRC serially in a group of low birth weight infants

  - Measurement of cardiac output in newborn infants using one of the new bloodless techniques

  - Application of the same methods as above for further delineation of the pathophysiology of aspiration pneumonia and the Wilson-Mikity syndrome.

- Lung Lecithin Synthesis--Normal and Asphyxial (FY 72: $78,564). The specific aims of this project are to:

  - Elucidate the pathways of surfactant synthesis

  - Study the relationship between intrauterine asphyxia and synthesis of the surfactant

  - Study the synthesis of surfactant in dogs whose tidal volume and respiratory rate have been increased by artificially enlarging the dead space.

- Respiratory Distress Syndrome in Infants (FY 72: $21,100). This contract supported study has as its purpose the comparison of two regimens of early treatment of respiratory distress syndrome (RDS). These treatments differ only in the concentration of oxygen (80% versus 40%) in the environment beginning at 1 hour of age until 6 hours of age. The arterial oxygen tension was carefully monitored and evaluated in order to insure adequate oxygenation and yet prevent the development of retrolental fibroplasia.

  See Section 1.1.H for description of additional related topic (Lung Maturation, Hormonal and Other Influences).

2.11.I Hyaline Membrane Disease of the Newborn--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.11.J Hyaline Membrane Disease of the Newborn--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

2.11.K Hyaline Membrane Disease of the Newborn--Bureau of Health Manpower Education

No identified ongoing BHME supported activities are related directly to this area.

2.11.L Hyaline Membrane Disease of the Newborn--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.11.M Hyaline Membrane Disease of the Newborn--Division of Research Resources

In FY 72, DRR supported four general clinical center grants with eight relevant components (FY 72: $171,780--%). These studies included:

- Wilson-Mikity syndrome (infants)
- Respiratory distress syndrome
- Therapy of respiratory failure
- Survival of respiratory failure with use of positive pressure ventilations
- Blood volume of newborn infants with respiratory distress syndrome

- Effect of O_2 and N_aHCO_3 at 1 hour of respiratory distress syndrome (human)
- Treatment of hyaline membrane disease (human)
- Prevention of hyaline membrane disease (human).

See Section 2.1.M for general discussion of DRR activities.

2.12 CYSTIC FIBROSIS

2.12.A Cystic Fibrosis--National Institute of Allergy and Infectious Diseases

One NIAID grant, (FY 72: $29,554), supports research which might result in findings applicable to cystic fibrosis. Scientists supported by this grant are investigating the variability in bactericidal and metabolic capacities--of human phagocytes--scavenger cells of importance in protection against disease. Emphasis will be placed on clinical application of research results, and various drugs (particularly antimalarials) will be evaluated for their effects on normal and abnormal phagocytes.

2.12.B Cystic Fibrosis--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area (FY 72: five grants, totalling $227,469--%).

Among the NIAMDD supported research related to this area are the following investigations:

- Cystic Fibrosis and Pulmonary Disease (FY 72: $25,048). This program project involves three studies:
  - The biochemistry of exocrine secretions
  - Tissue and organ culture studies
  - Bacteriology and antibacterial defense mechanisms in cystic fibrosis.

- Studies in Cystic Fibrosis (FY 72: $55,607). This program project is designed to:

  - Explore the basic defect in cystic fibrosis through biochemical, biophysical, and other methods

  - Evaluate and improve present therapeutic measures and investigate new methods with emphasis on pharmacologic agents

  - Study all recognizable clinical complications particularly in young adults--infertility in males, biochemical alteration in cervical mucus, diabetes mellitus, cirrhosis of the liver, as well as iatrogenic complications

  - Detect the heterozygote and further explore tissue analysis for biochemical alterations in the parents and siblings of children with cystic fibrosis and provide proper genetic counselling

  - Improve and test procedures for detecting cystic fibrosis, simply, accurately, and early

  - Better acquaint practising physicians and pediatricians with this disease, by arousing their suspicion to recognize cystic fibrosis early--prior to the development of irreversible pulmonary damage.

- Cystic Fibrosis--Identity of the Plasma Factor (FY 72: $11,352). This research project has a fourfold purpose:

  - The isolation in pure form of the plasma factor (which interferes with salt balance in normal tissues)

  - The preparation of an antibody to the plasma factor and development of an immune assay for the plasma factor

  - Preparation of a large quantity of the plasma factor using the quantitative immune assay

  - The preliminary chemical characterization of the factor.

If the correlation between presence of the factor in the plasma and the disease state is absolute, then the antibody will be used as the basis for a quantitative immune assay for rapid and accurate detection of the disease state.

2.12.C Cystic Fibrosis--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

2.12.D Cystic Fibrosis--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

2.12.E Cystic Fibrosis--National Institute of Environmental Health Services

No identified ongoing NIEHS supported research activities are related directly to this area.

2.12.F Cystic Fibrosis--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.12.G Cystic Fibrosis--National Institute of General Medical Sciences

No identified ongoing NIGMS supported research activities are related directly to this area.

2.12.H Cystic Fibrosis--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

2.12.I Cystic Fibrosis--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.12.J Cystic Fibrosis--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

2.12.K Cystic Fibrosis--Bureau of Health Manpower Education

For description of related manpower activities supported by BHME, see Section 2.3.K.

2.12.L Cystic Fibrosis--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.12.M Cystic Fibrosis--Division of Research Resources

In FY 72, DRR supported three general clinical center grants with three relevant components (FY 72: $27,090--%). These studies addressed:

- Corbenicillin and gentamicin for pulmonary infections in cystic fibrosis (human)
- Therapeutic evaluation of aerosol corbenicillin (children)
- Renal compensation to chronic respirator acidosis.

See Section 2.1.M for general discussion of DRR activities.

2.13 ACUTE AND CHRONIC RESPIRATORY FAILURE

2.13.A Acute and Chronic Respiratory Failure--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

2.13.B Acute and Chronic Respiratory Failure--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported research activities are related directly to this area.

2.13.C Acute and Chronic Respiratory Failure--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

2.13.D Acute and Chronic Respiratory Failure--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

2.13.E Acute and Chronic Respiratory Failure--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

2.13.F Acute and Chronic Respiratory Failure--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.13.G Acute and Chronic Respiratory Failure--National Institute of General Medical Sciences

The NIGMS funds and administers research related to the area of respiratory failure.

Among these NIGMS supported studies are:

- Development of Systems and Measurement Techniques for Assessing the Cardiorespiratory Status of Post-operative and Post-injury Patients (FY 72: $68,567). Funded and administered by the Biomedical Engineering Program, NIGMS, a respiratory cart for monitoring the status of patients with respiratory problems is currently being perfected.

- Mechanical Ventilation and Acute Respiratory Failure (FY 72: $10,551--%). This study is part of a broad-based multidisciplinary research program relevant to the discipline of anesthesiology and conducted by an NIGMS supported Research Center in Anesthesiology. Studies in pulmonary physiology conducted in this center focus on the effects of anesthesia, surgical procedures and associated changes in cardiopulmonary functions such as hypotension, hemorrhagic shock, hypoventilation, and hyperventilation.

- Blood Oxygen Binding Changes in Prolonged Respiratory Failure (FY 72: $13,385--%). This study is part of a broad-based multidisciplinary research program relevant to the discipline of anesthesiology. (See topic description above.)

2.13.H Acute and Chronic Respiratory Failure--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

2.13.I Acute and Chronic Respiratory Failure--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.13.J Acute and Chronic Respiratory Failure--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.)

2.13.K Acute and Chronic Respiratory Failure--Bureau of Health Manpower Education

For description of related manpower activities supported by BHME, see Section 2.3.K.

2.13.L Acute and Chronic Respiratory Failure--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.13.M Acute and Chronic Respiratory Failure--Division of Research Resources

In FY 72, DRR supported four general clinical center grants with four relevant components (FY 72: $62,703--%). These studies included:

- Body composition in respiratory failure (human)
- Assisted ventilation in treatment of respiratory failure
- Aggressive approach to treatment of respiratory insufficiency (human)
- Long-term effects of respiratory distress syndrome in adults.

See Section 2.1.M for general description of DRR activities.

2.14 EXTRAPULMONARY MANIFESTATIONS OF RESPIRATORY DISEASES

2.14.A Extrapulmonary Manifestations of Respiratory Diseases--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

2.14.B Extrapulmonary Manifestations of Respiratory Diseases--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported activities are related directly to this area.

2.14.C Extrapulmonary Manifestations of Respiratory Diseases--National Cancer Institute

The NCI funds and administers grant supported research related to this area (FY 72: $63,092):

- Acid-Base Electrolyte Balance in Neoplastic Disorders (FY 72: $31,851). This study investigates respiratory adjustment to changes in serum bicarbonate concentration induced by potassium or ammonium chloride administration in patients with chronic hypercapnia. The role of the extracellular bicarbonate concentration modifying the respiratory control mechanism is studied in patients with chronic hypercapnia. Additionally, the study considers the lipid content and palmitate incorporation in lungs of dogs with granulomatous disease--palmitic acid incorporation into lung phopholipids is measured in normal dogs and animals with granulomatous disease of the lung induced with Freund's adjuvant. The observations indicate that the phospholipid content per unit wet

weight, the uptake of labelled palmitic acid and its preferential incorporation into lecithin is not altered by granulomatous disease of the lung.

- Virus, Vitamin A and Carcinogen in Respiratory Cancer (FY 72: $31,241). In many parts of the world, the human respiratory tract is subjected to the kinds of influences to be investigated under this research: environmental carcinogens, nutritional deficiencies and successive respiratory virus infections. This investigation attempts to evaluate, in an experimental model, the possible synergism of these factors in inducing cancer of the upper respiratory tract.

2.14.D Extrapulmonary Manifestations of Respiratory Diseases--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

2.14.E Extrapulmonary Manifestations of Respiratory Diseases--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

2.14.F Extrapulmonary Manifestations of Respiratory Diseases--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

2.14.G Extrapulmonary Manifestations of Respiratory Diseases--National Institute of General Medical Sciences

No identified ongoing NIGMS supported research activities are related directly to this area.

2.14.H Extrapulmonary Manifestations of Respiratory Diseases--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

2.14.I Extrapulmonary Manifestations of Respiratory Diseases--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

2.14.J Extrapulmonary Manifestations of Respiratory Diseases--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

2.14.K Extrapulmonary Manifestations of Respiratory Diseases--Bureau of Health Manpower Education

No identified ongoing BHME supported activities are related directly to this area.

2.14.L Extrapulmonary Manifestations of Respiratory Diseases--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular and pulmonary diseases
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

2.14.M Extrapulmonary Manifestations of Respiratory Diseases--Division of Research Resources

In FY 72, DRR supported one general clinical center grant with one relevant component (FY 72: $10,637--%). The study addressed:

- Cardiopulmonary support in severe acute pulmonary disease (human).

See Section 2.1.M for general description of DRR activities.

III. BLOOD DISEASES

NHLI

III. BLOOD DISEASES

This section summarizes research activities (exclusive of intramural programs) supported in fiscal year 1972 (FY 72) by organizational components of the National Institutes of Health, exclusive of the National Heart and Lung Institute, in seven categories:

- Hemophilia and Other Bleeding Disorders (Section 3.1)
- Arterial Thromboembolism (Section 3.2)
- Disorders of Hemostasis Due to Platelet Abnormalities (Section 3.3)
- Venous Thrombosis and Pulmonary Embolism (Section 3.4)
- Thromboembolism in Relation to Prosthetic Devices (Section 3.5)
- Microcirculatory Thrombosis (Section 3.6)
- Hemoglobinopathies (Section 3.7).

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3.1 HEMOPHILIA AND OTHER BLEEDING DISORDERS

3.1.A Hemophilia and Other Bleeding Disorders--National Institute of Allergy and Infectious Diseases

A part ($41,151) of a larger NIAID award to an International Center for Medical Research (ICMR) supports investigations of anemia and bleeding disorders in West Pakistan. A principal objective of ICMR programs is to enable American Investigators to study international health problems that have an impact on the United States.

3.1.B Hemophilia and Other Bleeding Disorders--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area.

- A Study of Liver Intestinal and Nutritional Diseases (FY 72: $15,069--%). This program project includes among its studies:
  - An investigation of the mechanism of coenzyme B12, studied from a molecular point of view using ethanolamine ammonia-lyase
  - An investigation of coagulation and the liver, including a study of the molecular mechanism of action of vitamin K, investigation of the properties of a newly discovered system which destroys activated Factor V, and works on Factor XII-dependent kallikrein-bradykinin system in liver disease.

3.1.C Hemophilia and Other Bleeding Disorders--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

3.1.D Hemophilia and Other Bleeding Disorders--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

3.1.E Hemophilia and Other Bleeding Disorders--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

3.1.F Hemophilia and Other Bleeding Disorders--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

3.1.G Hemophilia and Other Bleeding Disorders--National Institute of General Medical Sciences

The NIGMS funds and administers research related to this area.

Research conducted in this area includes:

- A Study of Humoral Clotting Disorders (FY 72: $14,784--%). This investigation is conducted as part of a program project--NIGMS supported Clinical

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Genetics Center--and is concerned primarily with Factor VIII, hemophilia, and von Willebrand's disease.

- Automated Fluorescence Tests for Blood Clotting (FY 72: $22,360). This project involves:

  - A further exploration of existing quantitative methodology for measuring fibrin stabilizing factor (Factor XIII) in plasma--in regard to clinical applications

  - The development of an automated continuous type of rate assay for this.

3.1.H Hemophilia and Other Bleeding Disorders--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

3.1.I Hemophilia and Other Bleeding Disorders--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

3.1.J Hemophilia and Other Bleeding Disorders--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence

Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

3.1.K Hemophilia and Other Bleeding Disorders--Bureau of Health Manpower Education

BHME supported activities related directly to this area are described in Section 1.2.K.

3.1.L Hemophilia and Other Bleeding Disorders--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

An example of NLM supported activities categorically related to this area is a P.L. 480 funded project entitled A Critical Review: Organization of the Clotting Process.

3.1.M Hemophilia and Other Bleeding Disorders--Division of Research Resources

The Division of Research Resources (DRR) provides support for non-categorical resources to biomedical research

institutions in the support of categorical research activities of NIH.* DRR supports programs in four basic areas:

- General Clinical Research Centers Program. This program supports discrete clinical units (usually in university or university affiliated hospitals), which are utilized in the conduct of multicategorical clinical research

- Biotechnology Resources Program. This program supports the development and operation of large and complex technological resources (e.g., computer systems, electron microscopy service laboratories, mass spectrometry and nuclear magnetic resonance systems) for their application to biomedical research problems

- Animal Resources Program. This program provides support for the development and improvement of various animal models, including non-human primates, for use in biomedical research as well as the upgrading of institutional animal resources

- General Research Support Program. This program provides general research support to health professional and university graduate schools and other biomedical research organizations. (This program, in FY 72, derived its funds from separate appropriations to the National Institutes of Health and the National Institute of Mental Health; however, it was administered by DRR.)

The DRR funds and administers program project grants and general clinical research center grants which have components relevant to hemophilia and other bleeding disorders.

In FY 72, the DRR supported one animal resources program project which had a related research component (FY 72: $30,000).

* DRR funds resources which contributed to performance of studies documented in each DRR section.

In FY 72, the DRR supported 11 general clinical research center grants which had 14 related research components (FY 72: $274,166--8).

Supported activities include:

- Canine resource colony for a coagulation research. The DRR supports at Oklahoma State University a colony of dogs, normal and with various Factor VII, VIII, and IX deficiencies, for use by qualified investigators in the study of hemophilia
- Provision of clinical support for:
  - Studies of the effects of antihemophilic globulin and of antihemophilic factor metabolism
  - Studies of fibrinogen survival in coagulation disorders
  - Studies of treatment for circulation anticoagulants
  - Studies of transfusion in hemorrhagic diseases
  - Studies of problems in dental therapy for hemophilics
  - Studies of genetics.

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3.2 ARTERIAL THROMBOEMBOLISM

3.2.A Arterial Thromboembolism--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported activities are related directly to this area.

3.2.B Arterial Thromboembolism--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area (FY 72: one grant, totalling $41,374).

- A Study of Fibrinolytic Events in Human Tissues and Cells in Culture. This research project utilizes human tissues and cells in culture to investigate the chain of events which occurs at the cellular level after fibrin deposition and which leads to increased availability of plasminogen activator for the rapid disposal of fibrin on one hand, and to cell proliferation on the other. Culture models, developed for this purpose, facilitate the study of the identity and mode of action of factors which trigger or mediate these events.

3.2.C Arterial Thromboembolism--National Cancer Institue

For description of related research activities supported by NCI, see Section 3.3.C.

3.2.D Arterial Thromboembolism--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

3.2.E Arterial Thromboembolism--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

3.2.F Arterial Thromboembolism--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

3.2.G Arterial Thromboembolism--National Institute of General Medical Sciences

The Diagnostic Radiology Program, NIGMS, funds and administers projects for the development and application of new knowledge and techniques for the improved diagnosis of disease using ionizing and infrared radiation, radioisotopes and ultrasound.

Investigations have led to the development of new techniques for using radioisotopes and computer controlled radioactivity detectors to evaluate thromboembolism and microcirculation.

3.2.H Arterial Thromboembolism--National Instiute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

3.2.I Arterial Thromboembolism--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

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3.2.J Arterial Thromboembolism--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs.

Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

3.2.K Arterial Thromboembolism--Bureau of Health Manpower Education

BHME supported activities related directly to this area are described in sections 1.2.K and 3.3.K.

3.2.L Arterial Thromboembolism--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

3.2.M Arterial Thromboembolism--Division of Research Resources

IN FY 72, DRR supported one biotechnology resources grant which had a related research component (FY 72: $8,223--%) and three general clinical research center grants which had four related research components (FY 72: $51,930--%).

Included among the research are:

- Provision of computer support in a study of techniques to estimate thrombus size
- Provision of clinical support in:
  - The study of thrombolytic potential of streptokinase in arterial and venous occlusions
  - The study of thrombolytic therapy.

See Section 3.1.M for general description of DRR activities.

3.3 DISORDERS OF HEMOSTASIS DUE TO PLATELET ABNORMALITIES

3.3.A Disorders of Hemostasis Due to Platelet Abnormalities--National Institute of Allergy and Infectious Diseases

One NIAID award, (FY 72: $9,772) supports research on coagulation induced in rabbits by antigen-antibody complexes. In vitro studies have shown that immune complexes can shorten coagulation time; and, in specifically immunized animals, there is evidence of local coagulation when the appropriate antigen is added. Elucidation of the relationship between coagulation and immune complexes may lead to better treatment of individuals with diseases believed caused by deposition of antigen-antibody complexes in various body tissues.

3.3.B Disorders of Hemostasis Due to Platelet Abnormalities--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area (FY 72: four grants, totalling $90,319--%).

Among the NIAMDD supported studies related to this area are:

- A Study of Kinetics of Megakaryocyte and Platelet Turnover (FY 72: $29,596). The overall objectives of this project are to evaluate the kinetics of megakaryocytopoiesis in states of normal and perturbed thrombocytopoiesis and to study the nature of the feedback control of thrombocytopoiesis by the level of circulating platelets. The major emphasis at the present time is on:
  - The development of a bioassay system for thrombopoietin

- Investigation of the relationships between pluripotential hematopoietic stem cells and differentiated megakaryocytes.

- A Study of Lipid Metabolism in Mammalian Tissues (FY 72: $39,393). This research project includes:

  - A study of lipid metabolism in human blood platelets

  - The effects of thrombin and platelet aggregating agents on phospholipid biosynthesis in platelets.

  These studies also involve investigation of the structure of the platelet membrane and the effects of thrombin on platelet membrane proteins.

3.3.C Disorders of Hemostasis Due to Platelet Abnormalities--National Cancer Institute

In FY 72, the NCI funded and administered one program project grant which had components relevant to this area. These components are:

- Hemostatic Mechanisms (Human) (FY 72: $15,554--%). This is a component of a program grant "Clinical and Molecular Studies of Growth." The scope of the work in this component was not further identified.

- Thromboembolism (FY 72: $15,554--%). This is another component of the above program grant.

3.3.D Disorders of Hemostasis Due to Platelet Abnormalities--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

3.3.E Disorders of Hemostasis Due to Platelet Abnormalities--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

3.3.F Disorders of Hemostasis Due to Platelet Abnormalities--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

3.3.G Disorders of Hemostasis Due to Platelet Abnormalities--National Institute of General Medical Sciences

The NIGMS funds and administers research related to this area (FY 72: three grants, totalling $97,176--%).

Among these NIGMS supported investigations are:

- A Study of Collagen-Platelet Interaction on the Molecular Level (FY 72: $16,124). This study is part of a Trauma Center Program Project and is in line with the program project's goals in this area (i.e. to determine the degree to which abnormal bleeding or clotting is responsible for aggravating injuries and preventing recovery by studying coagulation changes following trauma; and to investigate the nature of microcirculation damage produced by intravascular clotting in specific organs and find means of reversing the resultant organ damage).

- A Study of Blood Platelets in Coagulation Disorders (FY 72: $14,784). This study is conducted within a Clinical Genetics Center.

3.3.H Disorders of Hemostasis Due to Platelet Abnormalities--National Institute of Child Health and Human Development

The NICHD funds and administers research related to this area (FY 72: one grant, totalling $27,246).

- Hemostasis and Hemorrhagic Diseases in Children. This research project is directed towards the study of the coagulation mechanism in low birth weight infants, especially those with the respiratory distress syndrome. Platelet aggregation is being studied in such infants, as well as those with iron deficiency anemia and recurrent epistaxis. The influence of drugs and infection on platelet aggregation and bacteremic shock and its relationship to disseminated intravascular coagulation are other topics being studied under this grant.

3.3.I Disorders of Hemostasis Due to Platelet Abnormalities--National Institute of Neurological Diseases and Stroke

The NINDS funds and administers research related to this area (FY 72: information regarding funding mechanism and level not available at time this report was prepared).

- Neonatal Polycythemia: A Manifestation of Chronic Injury During Distress and Outcome. The objective of this project is to study demographic and maternal factors associated with neonatal polycythemia.

  As part of the protocol during the NINDS Collaborative Study on Cerebral Palsy, capillary hematocrits were obtained as near to 48 hours as possible (generally between 36 and 60 hours) on 44,683 newborns, or 86 percent of all 77 and over were identified; and controls, matched for institution and year of birth, race, sex, socioeconomic index, and presence or absence of 4-year follow-up examination were selected randomly from all infants with 48-hour hematocrits 50 through 65. Various demographic and maternal factors were identified in both subjects and controls, and differences were statistically evaluated.

The subject cases (those with polycythemia manifested by hematocrits 77 and over) were found to have been the product of longer gestation, but were smaller in weight than the control population. There was an increase in incidence of placental pathology and the placenta of the subject cases was significantly lighter than the weights of the controls. One-minute and five-minute Apgar scores were both lower in the subject cases and there was a greater incidence of dysmaturity diagnosed in the subject cases. When compared with the whole Collaborative Study population, infants with polycythemia were noted to come from lower socioeconomic groups. Data suggest that neonatal polycythemia may be manifestation of chronic intrauterine distress.

A manuscript has been written for this study and is now in review for publication.

3.3.J Disorders of Hemostasis Due to Platelet Abnormalities--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

3.3.K Disorders of Hemostasis Due to Platelet Abnormalities--Bureau of Health Manpower Education

The BHME Division of Allied Health Manpower funds and administers programs related to the area of blood diseases (FY 72: one grant, totalling $19,714).

- Hematologic Morphology Instruction via Color Closed Current Television. This grant supported project is focused upon the development of self-instructional programs in hematology morphology for students of medical technology.

3.3.L Disorders of Hemostasis Due to Platelet Abnormalities--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

3.3.M Disorders of Hemostasis Due to Platelet Abnormalities--Division of Research Resources

In FY 72, the DRR supported 15 general clinical research center grants which had 16 related research components (FY 72: $251,820--%).

These grants all provide clinical support for research studies examples of which are identified below:

- Rheological studies
- Thrombocytopenic studies
- Coagulation abnormality studies
- Platelet disorder studies

- Bone marrow studies
- General hematological studies.

See Section 3.1.M for general discussion of DRR activities.

3.4 VENOUS THROMBOSIS AND PULMONARY EMBOLISM

3.4.A Venous Thrombosis and Pulmonary Embolism--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

3.4.B Venous Thrombosis and Pulmonary Embolism--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers a research study related to this area entitled, A Study of Fibrinolytic Events in Human Tissues and Cells in Culture. (See Section 3.2.B, Arterial Thromboembolism, for description of this project.)

3.4.C Venous Thrombosis and Pulmonary Embolism--National Cancer Institute

For description of related research activities supported by NCI, see Section 3.3.C.

3.4.D Venous Thrombosis and Pulmonary Embolism--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

3.4.E Venous Thrombosis and Pulmonary Embolism--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

3.4.F Venous Thrombosis and Pulmonary Embolism--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

3.4.G Venous Thrombosis and Pulmonary Embolism--National Institute of General Medical Sciences

The NIGMS funds and administers research related to this area. See Section 3.2.G, Arterial Thromboembolism, for description of research.

3.4.H Venous Thrombosis and Pulmonary Embolism--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

3.4.I Venous Thrombosis and Pulmonary Embolism--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

3.4.J Venous Thrombosis and Pulmonary Embolism--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International

Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

3.4.K Venous Thrombosis and Pulmonary Embolism--Bureau of Health Manpower Education

BHME supported activities related directly to this area are described in Section 3.3.K.

3.4.L Venous Thrombosis and Pulmonary Embolism--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

3.4.M Venous Thrombosis and Pulmonary Embolism--Division of Research Resources

DRR funded and administered one general clinical research center grant which had a component relevant to venous thrombosis and pulmonary embolism (FY 72: $13,217--%).

- Photocoagulation for complications of branch vein occlusion (human).

For description of additional related research activities supported by DRR, see Sections 3.2.M, 3.3.M; for general description of DRR activities, see Section 3.1.M.

3.5 THROMBOEMBOLISM IN RELATION TO PROSTHETIC DEVICES

3.5.A Thromboembolism in Relation to Prosthetic Devices--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

3.5.B Thromboembolism in Relation to Prosthetic Devices--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area (FY 72: seven contracts, totalling $603,779).

- Improved Nonthrombogenic Materials (FY 72: $95,200). The goals of this project are to:

  - Prepare a number of potential nonthrombogenic surfaces by grafting hydrophilic polymer chains to other polymeric substrates

  - Test such surfaces for blood compatibility *in vitro*; (the investigators will prepare a series of hydrogels of varying water content and test these by standard *in vitro* coagulation studies.

  To date the substrate material used for grafting has been polyethylene in the form of film or tubing. The grafting of hydrophilic monomers to polyethylene has been accomplished by two procedures. One involves irradiation of substrate in an aqueous solution of monomer. In the other, irradiation of the substrate is done in advance in an oxygen atmosphere.

The thrombogenicity of the materials has been evaluated *in vitro* by exposing the material to fresh whole human blood and measuring the partial thromboplastin time (PTT), Stypven time (ST), and thrombin time (TT) of the exposed blood. With the grafted films cell counts were also usually done. Polyethylene and siliconized glass were used as controls. From the results of the *in vitro* testing several grafted materials have emerged as promising. Dimethylaminoethyl methacrylate grafts have shown up well in both test systems. Both 2-sulfoethyl methacrylate grafts and sequential grafts of acrylic acid and 4-vinyl pyridine have given very good results in one test method. Vinyl pyrrolidone and acrylamide may also be of interest.

Further optimization of the grafts will be done and an extensive blood compatibility testing program will be developed with the goal of having a material well enough evaluated and characterized to be ready for clinical testing by the end of the fiscal year.

- Fluid Dynamics of Blood Cells (FY 72: $44,998). The objectives of this study are:

  - Analysis of blood velocity profiles in narrow channels using a 3-D microscope system
  - Study of hematocrit skimming layers using fluid conductivity measurements
  - Couette skimming layer force evaluation
  - Analysis of flow-enhanced diffusion coefficients using the Taylor Dispersion method
  - Performance of electron and phase microscopy studies of formed element behavior following wall contact.

- Antithrombogenic Surfaces: Platelet-Interface Relations (FY 72: $51,500--%). This investigation is designed to study the composition of the layer of plasmatic components adsorbed to materials exposed to blood, and to characterize this layer as to its effect on blood platelets.

  Major findings to date indicate that there are morphological differences between the adsorbed layers formed on certain polymeric and nonpolymeric test materials and that an adsorbed layer is universally present between adherent platelets and the surface of the test material. It appears that it is this adsorbed layer and not the surface of the test materials which determines thrombogenicity. The chemical nature of the test material may control the composition of the adsorbed layer and through this, its thrombogenicity, or it may merely control the rate of deposition of the adsorbed layer.

  This investigation is continuing the characterization of the blood-polymer layer and its role in material thrombogenicity. There will also be an evaluation of various polymers in an *in vivo* situation by placing vena cavae rings in Rhesus monkeys.

- Research and Development of Cannulas and Nonthrombogenic Materials (FY 72: $56,500--%). The objectives of this study are to:

  - Develop, fabricate, and evaluate a useful cannula for subcutaneous insertion between the arterial and venous ends of vessels

  - Continue investigation of dacron velour with appropriate diameter and thicknesses for inhibition of infections

  - Investigate coating of silastic cannulas with nonthrombogenic materials.

Major findings to date have shown that the end to side anastomosis is apparently not feasible in small peripheral arteries with this investigating group.

Prototypes of the proposed cannulae are being fabricated and will undergo modification and in vivo testing in laboratory animals in the ensuing months.

- Identification of a Nonthrombogenic Environment (FY 72: $169,700). The objective of this study is to identify those characteristics of surfaces and blood which make an atraumatic nonthrombogenic environment possible.

  To date, two intravascular test devices have been designed to permit in vivo testing of artificial materials under controlled blood velocities. Particular parts of the device are isolated from contact with possibly damaged intima and consequent release of tissue thromboplastin. The role of various surfaces, turbulent flow, platelets, coagulation factors, temperature, and blood velocity on the initiation of clotting are being investigated. Various histologic chemical and physical manifestions of clotting are being measured. The effects of aspirin and methylene blue on clotting are also being studied.

- Blood Flow Considerations to Minimize Thrombosis in Artificial Kidney Systems (FY 72: $97,981). The objective of this study is to investigate hydromechanical and surface materials properties relevant to initiation and propagation of thrombus formation

  To date, the formation of thrombus in the separated flow region has been found to vary with the shear rate of the particular test chamber. Aggregation and subsequent thrombus formation occur more rapidly as the shear rate of the particular chamber increases. This effect scales in the opposite direction to results obtained in the simple stagnation point flow previously studied. Experiments have been continued in order to further define and understand the influence of a separated flow region on thrombus formation.

Experiments have also been completed to investigate thrombus formation in a tube flow configuration. These experiments have indicated the importance of properly controlling the entrance configuration to the tube. As result of these experiments a new entrance configuration has been designed and will be employed. Subsequent studies will:

- Investigate blood-surface interfacial phenomena under controlled flow conditions as a function of systematically controlled surface properties of polyurethane test surfaces and systemic anticoagulation

- Investigate the influence of locally infused thrombus inhibiting agents as a means of controlling or eliminating thrombus formation in shunts or dialyzers.

- Nonthrombogenic Surfaces and Artificial Kidney Design (FY 72: $87,900). The objective of this study is to develop nonthrombogenic surfaces for a pilot model of an artificial kidney.

Studies of nonthrombogenicity of formaldehyde-glutaraldehyde-hydrogels covalently bonded with heparin indicate that they are materials of low thrombogenicity. In vivo studies, including A-V shunts on dogs, and rings in the inferior vene cava according to the Gott model, both fixed and floating, indicate that covalently heparinized surfaces will not be practical for the large areas of artificial kidney devices unless these surfaces are previously coated with serum albumin, to avoid platelet attraction.

In vitro tests by themselves are necessary but insufficient for predicting ultimate in vivo performance. (The covalently heparinized hydrogels that have been tested, even without prior exposure to albumin, exhibit excellent performance in in vitro tests: all blood clotting times exceed 50 minutes, no elutable heparin is found, insignificant plasma proteins are adsorbed, and blood clots normally when transferred from test tubes to standard activating surfaces.)

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Hydrogel membranes have been greatly improved by casting the reacting solutions on the nonwoven nylon fabric Cerex (TM: Chemstrand). Hydrogel membranes (5.3 mils) show equal resistance to sucrose (100 min/cm) as 1.1 Cuprophane and twice the resistance to urea (32 versus 17 min/cm). Potentially useful tubing and other hardware have been prepared by modifications of the original casting syrup. (It should be noted that although the surface properties of heparinized hydrogels are promising, their mechanical properties are poor.)

3.5.C Thromboembolism in Relation to Prosthetic Devices--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

3.5.D Thromboembolism in Relation to Prosthetic Devices--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

3.5.E Thromboembolism in Relation to Prosthetic Devices--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

3.5.F Thromboembolism in Relation to Prosthetic Devices--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

3.5.G Thromboembolism in Relation to Prosthetic Devices--National Institute of General Medical Sciences

The NIGMS funds and administers research related to this area. See Section 3.2.G, Arterial Thromboembolism, for description of research.

3.5.H Thromboembolism in Relation to Prosthetic Devices--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

3.5.I Thromboembolism in Relation to Prosthetic Devices--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

3.5.J Thromboembolism in Relation to Prosthetic Devices--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

3.5.K Thromboembolism in Relation to Prosthetic Devices--Bureau of Health Manpower Education

No identified ongoing BHME supported activities are related directly to this area.

3.5.L Thromboembolism in Relation to Prosthetic Devices--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

3.5.M Thromboembolism in Relation to Prosthetic Devices--Division of Research Resources

The DRR funded and administered three general clinical research center grants which had three components relevant to thromboembolism in relation to prosthetic devices (FY 72: $40,488--%). These studies relate to platelet survival in prosthetic heart valves and hemolytic effects of cardiovascular prothesis in humans.

See Section 3.1.M for general discussion of DRR activities.

3.6 MICROCIRCULATORY THROMBOSIS

3.6.A Microcirculatory Thrombosis--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

3.6.B Microcirculatory Thrombosis--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported research actitivies are related directly to this area.

3.6.C Microcirculatory Thrombosis--National Cancer Institute

For description of related research activities supported by NCI, see Section 3.3.C.

3.6.D Microcirculatory Thrombosis--National Institute of Dental Research

The NIDR funds and adminsters research related to this area (FY 72: one grant, totalling $22,617.)

- Gingival tissue fibrinolysis and heparin (no project description available at time report was prepared).

3.6.E Microcirculatory Thrombosis--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

3.6.F Microcirculatory Thrombosis--National Eye Institute

The NEI funds and administers research related to this area.

- Studies on the Posterior Segment of the Eye (FY 72: $35,000). Includes examination of the role of platelet aggregation in the pathogenesis of diabetic retinopathy and the resultant closure of blood vessels by platelet aggregates.

3.6.G Microcirculatory Thrombosis--National Institute of General Medical Sciences

The NIGMS funds and administers research related to this area

- See Section 3.2.G, Arterial Thromboembolism, for description of research.

3.6.H Microcirculatory Thrombosis--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

3.6.I Microcirculatory Thrombosis--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

3.6.J Microcirculatory Thrombosis--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

3.6.K Microcirculatory Thrombosis--Bureau of Health Manpower Education

No identified ongoing BHME supported activities are related directly to this area.

3.6.L Microcirculatory Thrombosis--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and and blood resources.
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

See Section 3.1.L for example of NLM supported activity categorically related to this area.

3.6.M Microcirculatory Thrombosis--Division of Research Resources

In FY 72, DRR supported two general clinical research center grants which had two related research components (FY 72: $29,874--%):

- Hypercoagulability and thrombosis
- Intravascular coagulation in renal disease.

See Section 3.6.M for general discussion of DRR activities.

3.7 HEMOGLOBINOPATHIES

3.7.A Hemoglobinopathies--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

3.7.B Hemoglobinopathies--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area (FY 72: 56 grants, totalling $2,885,130--%).

Among the NIAMDD supported research in this area are the following projects:

- A Study of Biochemistry and Immunology of Blood Diseases (FY 72: $17,450--%). This program project includes investigation of:
  - Dissociation-association of heme proteins
  - Oxygen dissociation in human hemoglobinopathies and the binding of 2,3 DPG to hemoglobin
  - Studies on iron absorption
  - Chemotherapy of hematologic malignancies.
- Research and Hereditary Clinic (FY 72: $50,280--%). This program project includes the following studies related to this area:
  - Possible detection and evaluation of enzyme and hemoglobin abnormalities in patients with hemolytic disorders
  - Evaluation of different therapeutic regimens for sickle cell anemia
  - The pathophysiology of the sickle cell trait.

- Hemoglobin Variants in Relation to Disease (FY 72: $58,830). This research project includes among its objectives:

  - The conduct of a survey of the incidence of abnormal hemoglobins in umbilical cord blood samples

  - Studies of intraerythrocytic hemoglobin precipitations which are demonstrable in dark field microscopy with mercury lamp illumination

  - The development of a micromethod of quantitative evaluation of globin chains--normal and abnormal.

- Energy Metabolism of the Erythrocyte (FY 72: $38,262) This research project includes studies concerned with the state of the intracellular hemoglobin in regard to the hydration of the protein or hemoglobin-water interactions.

- Glutathione Instability with Other Red Cell Defects (FY 72: $29,556). This research project involves a study of the incidence, variation, and inheritance patterns of various red blood cell enzymes. Red blood cell enzyme abnormalities are being sought for in children with various chromosomal abnormalities in an attempt to obtain information on gene localization. Interrelationship between enzyme defects and disease are being studied as is the linkage between hereditary enzyme defects and other hereditary disorders.

- Genetic Control of Hemoglobin Synthesis (FY 72: $45,850). This research project has as its major objective the selective control of the synthesis of individual hemoglobins.

- Inherited Variations in Human Blood Components (FY 72: $47,078). This research project is designed to study the genetic polymorphisms in blood and other tissues to obtain information about:

  - The effects of structural alteration on molecular function

  - The effects of such molecular functional changes on overall physiology

- The applicability of genetic variants to mapping the human chromosomes to other uses of genetic markers

- The association between apparently benign molecular variation and susceptibility to disease.

- Physical Chemistry of Human Hemoproteins (FY 72: $11,904). This research project has, as its overall aim, the investigation of the molecular physiology of normal and abnormal hemoproteins. This study is designed to correlate the changes in chemical reaction rates and thermodynamic values for these reactions with the concentrations of polyvalent anions (such as DPG and ATP) and polyvalent cations (such as calcium ion). The specific type of reactions being studied include aggregation phenomena as well as classical ligand reactions.

- Abnormalities of Hemoglobin Metabolism (FY 72: $47,185). This research has as its main objective the elucidation of abnormalities of hemoglobin metabolism in thalassemia and related disorders, including hereditary anemias of mice, and the anemia of Belgrade rats.

- Studies of Sickling Mechanisms and Minor Hemoglobins (FY 72: $60,287). This research project is designed to further elucidate the molecular mechanisms of erythrocyte sickling: to ascertain the nature and location of binding sites between molecules involved in polymerization of deoxy-Hbs, the role of non-S hemoglobins in sickling interactions and factors which can modify sickling.

- Chemistry of Sickle Cell Anemia Variants (FY 72: $88,874). This research project encompasses:

  - Characterization of hemoglobin from individuals who are thought to have sickle cell anemia of a variant atypical mild form and/or unusually long survival

  - Elucidation of structure-function interrelationship of alpha and beta polypeptide chains in the sickling phenomenon as revealed by other naturally selected (genetic) amino acid substitutions found in association with the presence of homozygous beta S chains

- Chemical modification of hemoglobin S as a potential treatment of sickle cell disease

- Characterization of hemoglobin S obtained during clinical trials of therapy for sickle cell vaso-occlusive crisis and correlation of the clinical and chemical data.

In addition, within the NIAMDD funded and administered research related to hemoglobinopathies is research related to thalassemia (Cooley's Anemia) (FY 72: 18 projects, totalling $583,997).

These NIAMDD sponsored projects can be grouped in two categories--those whose primary emphasis is in this area (FY 72: six projects, totalling $192,938) and those with secondary emphasis in this area (FY 72: 12 projects, totalling $391,059).

Within the former group are the following projects:

- Hemoglobin mRNA in Thalassemia (FY 72: $18,305). This research project involves the attempt to isolate messenger RNA from reticulocytes of patients with thalassemia and other hemoglobinopathies. The RNA is digested enzymatically and the 5' OH of oglionucleotides is labelled with polynucleotide kinase. The nucleotide sequence of the oligonucleotides is then fractionated and analyzed. Attempts will be made to characterize the portions of the RNA preceding the initiator cordon for globin synthesis.

- Intermediate Steps in Hemoglobin Synthesis (FY 72: $25,053). This research grant supported project is concerned with the characteristics of hemoglobin synthesis in various thalassemia syndromes, hemoglobinopathies, and certain other hereditary and acquired anemias in which a deficit in hemoglobin synthesis might be present. Investigations to characterize structurally and functionally newly detected mutant hemoglobins are also being performed.

- Lysis of Red Cells by Hemoglobin and Membrane Disease (FY 72: $55,210). This research project involves the utilization of metabolic dysfunctions in human and selected animal erythrocytes and granulocytes to investigate normal physiologic functions and to determine the pathophysiology of human disease--with the ultimate purpose being to define better methods to deal therapeutically with inherited disorders of the blood.

- Molecular Basis of Thalassemia (FY 72: $30,605). This research project is directed toward the elucidation of the molecular basis of unbalanced globin synthesis in thalassemia. It will be determined whether the affected globin messenger is functionally abnormal or produced in a low amount in beta and alpha thalassemia syndromes. In addition, this investigation is:

  - Studying the basis of balanced globin synthesis in thalassemia trait marrow as opposed to peripheral blood

  - Attempting to sequence and identify abnormal nucleotides in thalassemic globulin messenger RNA

  - Investigate the mode of action and possible therapeutic value of drugs vital in protein synthesis which may induce improved balance of globin synthesis in these syndromes.

- Thalassemia and Hemoglobinopathies (FY 72: $17,300). No description of this project was available at the time this report was prepared.

- Hemoglobin Metabolism in Thalassemia (FY 72: $46,465). The main objective of this research is to elucidate abnormalities of hemoglobin metabolism in thalassemia and related disorders. Specific studies include investigation of the chemical structure and metabolic origin of excreted dipyrroles in these disorders. Other animal experiments include 59 Fe and C14-glycine *in vivo* and *in vitro* labelling to investigate hemoglobin synthesis and catabolism. In addition, heme and pyrrole metabolism is being investigated in the mammalian fetus.

Among the NIAMDD funded research with secondary emphasis in thalassemia are the following projects:

- Protein Synthesis in Erythroid Precursors (FY 72: $8,980). The object of this study is to investigate the regulation of hemoglobin synthesis by human erythroid precursors. Immature hemoglobin synthesizing red cells are being obtained from normal individuals and patients with thalassemia and hemoglobinopathies --and the processes of globin chain initiation and translation are being compared.

- Regulation of Hemoglobin Synthesis (FY 72: $27,985). No description of this project was available at the time this report was prepared.

- Heme and Globin Synthesis in Infants and Children (FY 72: $35,803). The principal goal of this project is to provide a greater understanding of hemoglobin synthesis in the thalassemia syndromes, the hemoglobinopathies, and normal infants and children. This includes studies of:

  - Abnormalities causing a variety of unusual forms of thalassemia

  - Globin synthesis in disorders involving sickle and other variant hemoglobins

  - The role of the free alpha chain in the control of hemoglobin synthesis

  - The inhibition of globin attachment to the red cell membrane

  - Acquired thalassemia-like defects.

  The long-range objective of these studies is to provide information of use in accurate genetic counselling and treatment of human hemoglobinopathies.

- Studies of the Genetic Aspects of Hemoglobin Synthesis (FY 72: $39,855). This research project is attempting to determine:

  - Whether thalassemia syndromes are usually due to a deficiency of messenger RNA for the hemoglobin chain

- How much information exists in the hemoglobin messenger RNA which is not used to encode the protein chain, but is necessary for start and stop signals or binding sites for enzymes and ribosomes.

3.7.C Hemoglobinopathies--National Cancer Institute

In FY 72, the NCI funded and administered research related to this area.

- Physiological Genetics of the Mouse (FY 72: $110,248). Highly congenic mice with and without mutant genes with clear-cut effects are being used to analyze gene action leading to at least six different hereditary anemias (W series, Sl series, Hertwig's anemia, flexed, microcytic, and "few clones"). Early embryonci stages will be studied and developmental changes will be followed to the full adult stage (60 to 90 days) when available. Responses to hemopoietic stresses (hypoxia, bleeding, phenylhydrazine injection, and whole-body irradiation) will be compared in adult normal mice and mice with each type of severe hereditary anemia. The structural nature of genetic control of hemoglobin polymorphisms in adult normal mice is being investigated. Search will continue for the position in the genetic linkage map of the Hba locus, controlling the structure of the hemoglobin alpha-chain. The hemoglobins of mice from rare inbred strains of independent origin are being studied to search for hitherto undescribed genetic variants. Popp's hypothesis that many mice have duplicated alpha-chain cistrons will be tested and the nature of beta-chains produced under the control of the rare Hbb super P allele will be studied.

In addition the NCI funds and administers research related specifically to thalassemia (Cooley's Anemia):

- Control of Hemoglobin Synthesis by Erythroid Cells (Human) (FY 72: $30,039--%). This project is focused upon problems related to thalassemia (Cooley's Anemia).

- Cancer Clinical Research--Relation of Inherited Antigens to Cancer Susceptibility in Man. (No FY 72 funding level or project description was available at the time this report was prepared. The NIH Division of Research Grants Research Documentation Section indicated the relevance of this project to the area of thalassemia.)

3.7.D Hemoglobinopathies--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

3.7.E Hemoglobinopathies--National Institute of Environmental Health Sciences

In FY 72, NIEHS funded and administered a program project, one component of which entitled, "Impact of Nitrates on Particularly Susceptible Population" is related to this area (FY 72: $13,876--%).

3.7.F Hemoglobinopathies--National Eye Institute

The NEI funds and administers research related to this area.

- Retinal Circulation Times (See Section 1.5.F for description of this project). One objective of this project is to obtain quantitative data concerning the physiology of retinal circulation in sickle cell disease, comparing this with the "normal" state. (Factors measured are: retinal circulation times, retinal arteriolar mean velocities, retinal arteriolar volume flow, and expansile pulsations.)

1.7.G Hemoglobinopathies--National Institute of General Medical Sciences

The Genetics Program NIGMS, funds and administers grant supported studies in this area.

The investigations supported include:

- A Project on the Cyanate Treatment of Sickle Cell Anemia (FY 72: $13,900). This project is conducted as part of the NIGMS Genetics Centers at the University of Washington, Seattle. The project design involves the relation of the oxygen dissociation curve of sicle cell hemoglobin to various partial pressures of oxygen, both without the addition of cyanate and in the presence of cyanate. Additional studies conducted in this project within the Genetics Center include work on the effect of carbamylation of the alpha- and beta-chains of human hemoglobin as well as reconstituted chains, and on erythocyte isozymes which show altered electrophoretic mobility after carbamylation. Chronic toxicity studies of cyanate in monkeys are also to be performed.

- A project, within the Genetics Centers, University of Washington, Seattle, which involves a study of the development of hemoglobin in man, the oxygen dissociation and other functions of embryonic hemoglobins, the structural determination of the isozymes of red cells with hemoglobin variants, and several aspects of beta thalassemia. These studies were supported at a level of $94,501 during FY 72.

- A program for screening and counselling for sickle cell trait is being supported for one year at the NIGMS Genetics Center at Seattle (FY 72: $28,000--%). This program involves:

  - Familiarization of medical and paramedical personnel, teachers, social workers and other professionals with the problems

  - An evening course dealing with the genetic, social and medical aspects of the problem

- Intensive training of laboratory personnel in sickle cell detection.

- Intensive training of selected public health nurses or similar individuals in genetic aspects and counselling

- Actual screening in schools and other areas where young people congregate.

- A study of the rates at which normal and abnormal hemoglobins are produced is a subproject part of a program project grant at the University of Michigan, Ann Arbor. This study is being conducted in an attempt to obtain a better understanding of the genetic basis for the regulation of hemoglobin production in normal as well as diseased states, such as thalassemia. Also being studied are structure-function relationships of hemoglobin, and physiologic investigations of sickle cell anemia. This group of projects was supported at a level of $97,883 during FY 72.

- A study of thalassemia is one subproject component of a program project at Columbia University. Investigators working on this study have obtained evidence for the presence of a dialyzable inhibitor of alpha-chain synthesis and stimulator of beta-chain synthesis. They have also discovered that proteolysis appears to be a major means of removal of excess alpha-chains in beta thalassemia. The investigators are sequencing the beta-chain in thalassemia for possible amino acid substitutions, and are also using a cell-free system to determine whether beta thalassemia is due to a deficiency or absence in messenger RNA. This work was supported at the level of approximately $15,000 in FY 72.

The Pharmacology-Toxicology Program, NIGMS, funds and administers a large center program (FY 72: $716,090) which includes a basic study devoted to heme synthesis and the role of cytochrome P-450. These studies, which are devoted to a basic understanding of control mechanism within the cell, may have some application in the treatment of some hemoglobin disorders.

This program also funds and administers grant supported research devoted to understanding the mechanism of drug-induced hemolysis (FY 72: $33,690). The projected program includes the specific identification of primaquine metabolites in urine or in liver microsomal preparations, and a measurement of their levels in the circulation. Also to be examined are the effects of the drug metabolites on the red cell membrane. It is hoped that these studies will lead to the development of model systems which will have a predictive value for drug-induced hemolysis.

Related specifically to thalassemia (Cooley's Anemia), NIGMS funds and administers research. Each research project related to this area is an identifiable component of a larger program project or center grant. Among the NIGMS funded research related to this area are the following projects:

- The Molecular Defect in Thalassemia (FY 72: $17,601--%). This is part of a large multidiscipline study of the mechanisms controlling normal and abnormal cell differentiation and development. Experiments are designed to investigate regulatory mechanisms of normal and abnormal hemopoietic cell differentiation in man (normal subjects and patients with thalassemia), rabbit, and adult and fetal mice.

- Genetic Studies in Thalassemia (FY 72: $17,601--%). (Description as above.)

- Abnormal Hemoglobins (FY 72: $17, 601--%). (Description as above.)

- Genetics in Medicine--Gene Action in Man: This program project involves several research projects related to this area:

  - A study of hemoglobin variants (FY 72: $27,942--%)

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- Isolation and base sequence of normal and mutant mRNA (FY 72: $27,942--%)

- Hemoglobin development in man (FY 72: $27,942--%)

- A study of thalassemia (FY 72: $27,942--%)

- A search for thalassemia-like syndromes in nonhuman primates (FY 72: $27,942--%)

- Population studies of genetic counselling (FY 72: $27,942--%).

- Genetic Regulation of Hemoglobin Structure and Synthesis (FY 72: $66,268--%). This study is one investigation within a program project in Human Biochemical Genetics, the major objective of which is to further the understanding of normal and abnormal gene function in human cells at various levels of biological organization.

  See also project descriptions in this section for "A Study of Thalassemia" and "A study of the rates at which normal and abnormal hemoglobins are produced."

3.7.H Hemoglobinopathies--National Institute of Child Health and Human Development

NICHD funds and administers two research grants related to hemoglobinopathies:

- Pathophysiology of Fetal Hemoglobin Synthesis (FY 72: $32,294). This project deals with problems of embryonic and fetal hemoglobin synthesis in mouse and man. Research aims include:

  - Elucidation of the hemalologic potential of the cells of the mouse yolk sac

  - Development of a cell-free synthesis of hemoglobin F from embryonic human livers

  - Study of the effects of gamma-chain synthesis, and various hormones on HbF.

Also included in this research grant are studies on the possible translational control of fetal hemoglobin synthesis employing fetal polysomes and adult supernatant factors as well as adult polysomes and fetal supernatant material.

- The Synthesis of Fetal and Adult Hemoglobins (FY 72: $49,507). This investigation is concerned with defining the role of 8', 5' - cyclic adenosine monophosphate in the switch from one hemoglobin type to another and, in particular, from fetal to adult hemoglobin synthesis. This is being approached through isolation and study of cyclic mucleotide dependent protein kinases from rabbit reticulocytes, human cord blood, sheep bone marrow and reticulocytes. The kinase system in thalassemias is also being examined.

3.7.I Hemoglobinopathies--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

3.7.J Hemoglobinopathies--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

3.7.K Hemoglobinopathies--Bureau of Health Manpower Education

BHME supported activities related directly to this area are described in Section 3.3.K.

3.7.L Hemoglobinopathies--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources.
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

3.7.M Hemoglobinopathies--Division of Research Resources

In FY 72, the DRR supported 37 general clinical research center grants with 52 relevant components (FY 72: $1,094,855--[illegible] These studies included:

- Anemic Disorders--as represented by chemolytic anemia, congenital hemlytic anemia, pernicious anemia, and hypochromic microcytic anemia
- Hemoproteins (human)
- Sickle Cell Anemia
- Thalassemia.

See Section 3.1.M for general description of DRR activities.

IV. BLOOD RESOURCES

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IV. BLOOD RESOURCES

This section summarizes research activities (exclusive of intramural programs) supported in fiscal year 1972 (FY 72) by organizational components of the National Institutes of Health, exclusive of the National Heart and Lung Institute, in six categories:

- Blood Collection (Section 4.1)
- Fractionation and Preservation (Section 4.2)
- Laboratory Procedures and Controls (Section 4.3)
- Utilization (Section 4.4)
- Systems Management (Section 4.5)
- Transplantation (Section 4.6).

4.1 BLOOD COLLECTION

4.1.A Blood Collection--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

4.1.B Blood Collection--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported activities are related directly to this area.

4.1.C Blood Collection--National Cancer Institute

In FY 72, the NCI funded and administered one contract which is relevant to this area:

- Procure human sera from defined population groups. No project description was available (FY 72: $22,490).

4.1.D Blood Collection--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

4.1.E Blood Collection--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

4.1.F Blood Collection--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

4.1.G Blood Collection--National Institute of General Medical Sciences

No identified ongoing NIGMS supported activities are related directly to this area.

4.1.H Blood Collection--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

4.1.I Blood Collection--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

4.1.J Blood Collection--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

4.1.K Blood Collection--Bureau of Health Manpower Education

BHME supported research activities related to this area are described in Section 3.3.K.

4.1.L Blood Collection--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

4.1.M Blood Collection--Division of Research Resources

The Division of Research Resources (DRR) provides support for non-categorical resources to biomedical research institutions in support of categorical research activities of NIH.* DRR supports programs in four basic areas:

- General Clinical Research Centers Program. This program supports discrete clinical units (usually in university or university affiliated hospitals), which are utilized in the conduct of multi-categorical clinical research

* DRR funds resources which contributed to performance of studies documented in each DRR section.

- Biotechnology Resources Program. This program supports the development and operation of large and complex technological resources (e.g., computer systems, electron microscopy service laboratories, mass spectrometry and nuclear magnetic resonance systems) for their application to biomedical research problems

- Animal Resources Program. This program provides support for the development and improvement of various animal models, including nonhuman primates, for use in biomedical research as well as the upgrading of institutional animal resources

- General Research Support Program. This program provides general research support to health professional and university graduate schools and other biomedical research organizations. (This program, in FY 72, derived its funds from separate appropriations to the National Institutes of Health and the National Institute of Mental Health; however, it was administered by DRR.)

No identified ongoing DRR supported research activities were applicable directly to the area of blood collection.

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4.2 FRACTIONATION AND PRESERVATION

4.2.A Fractionation and Preservation--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

4.2.B Fractionation and Preservation--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area (FY 72: one grant, totalling $62,224).

- Biosynthesis and Degradation of the Human Blood Group Substances. This research project has as its objective the change of serological specificity of the A and B blood and the making available of a Universal Donor type. This can be done by the use of enzymes involving specific degradation (glycosidases) or biosynthetic pathways (glycosyl transferases). This entails the study of immunochemistry and genetics of blood group substances, purification of enzymes involved and testing the effect of these enzymes on the physiological integrity and viability of erythrocytes.

4.2.C Fractionation and Preservation--National Cancer Institute

In FY 72 the NCI funded and administered seven research grants relevant to this area.

- Procurement of Fresh Blood Platelets for Clinical Use (FY 72: $75,725). This project is concerned with the preparation of fresh human platelet concentrates in connection with clinical research programs which include

intensive chemotherapy and/or radiotherapy as a part of the total care of patients with acute leukemia or other neoplastic disease.

Platelets are collected by plasmapheresis and prepared as unmodified concentrates. Clinical studies include evaluation of HL-A histocompatibility, and the hemostatic effectiveness of low-dose platelet transfusions. Other studies will be directed to improvements in platelet preparation and preservation, with particular respect to the clinical effectiveness of platelet concentrates following short-term storage under various conditions.

Parallel studies will be undertaken on the collection, preservation, and evaluation of normal human granulocyte concentrates prepared by "filtration leukopheresis."

- Leukemia Center (Platelet) Program (FY 72: $56,195). The transfusion of fresh blood components, particularly blood platelets, in children with cancer has reduced the frequency of hemorrhage due to disease or therapy. The purposes of this project are: to provide sufficient platelets for children receiving cancer therapy; to study the efficacy of these transfusions in a variety of circumstances; to develop more precise indications for platelet transfusion; and to elucidate factors which affect the survival, function and structure of platelets. Both clinical studies in children with cancer and studies in laboratory animals are employed.

- Separation of Blood by Continuous Flow Centrifuge (FY 72: $41,541). The antibacterial and circulating granulocyte responses of agranulocytic dogs to single infusions of granulocytes have been quantitated. These studies are being extended by examining the effect of repeated infusions in maintaining levels of circulating granulocytes and in preventing infection.

  The effect of histocompatibility differences between granulocyte donor and recipient will be studied.

  The evaluation of techniques for storing granulocytes will be continued. There will be an increasing emphasis on clinical studies. These are being

designed to test the feasibility of maintaining circulating granulocyte levels of agranulocytic patients. When these studies are complete, a controlled study will be conducted of the degree of protection against infection afforded by granulocyte maintenance.

Continuous plasma exchange for the treatment of hepatic coma continues to give encouraging results and this work will continue.

- Leukemia Center Platelet Program (FY 72: $180,079). Studies on a new approach to separation and harvesting of normal granulocytes using selective filtration-pheresis instead of centrifugation-pheresis are ongoing. These include an investigation of the viability and functional properties of the cells. A large scale study of the clinical value of granulocyte transfusions in general and filtered granulocytes in particular will be carried out. The mechanism of selective adhesion-elution of normal granulocytes will be studied with view of applying the filtration-pheresis approach to the harvesting of other blood elements for the purpose of transfusion. Preservation of normal granulocytes separated by filtration-leukopheresis will also be investigated.

- Leukemia Center Platelet Program (FY 72: $81,574). The objective of this Research Proposal is:

  - To evaluate those factors responsible for normal platelet survival and to determine possible differences in platelets obtained from different donors with special attention to the drugs that donor may have taken

  - To investigate those factors that will permit platelets to maintain ATP levels and to function after storage.

  Time, plasma anticoagulant, oxygen availability and storage temperature will be evaluated for their effect on platelet ATP levels and metabolic activity in vitro, especially in relation to activity of the Kreb's citric acid cycle and to platelet levels of cyclic AMP. The relation between platelet function in vitro and survival of platelets post-transfusion will be used to determine factors essential for more

efficient platelet storage. As a result, a realistic evaluation of the benefits of platelet transfusion therapy in severely thrombocytopenic leukemic patients and the determination of major factors and mechanisms that influence these benefits will be possible.

- Leukemia Center Platelet Program (FY 72: $95,104). This is a broad-based program designed to investigate the best methods of platelet transfusional support in cancer patients.

  Preliminary studies on platelet storage have indicated that Dimethylsulfoxide (DMSO) used as the cryoprotective agent permits maintenance of platelet viability after freezing and thawing of platelet concentrates. Further efforts will be directed at finding techniques to remove the DMSO prior to platelet transfusion and to investigate whether cryoprotective agents other than DMSO can be used.

- A New Human Blood Factor--Purification (FY 72: $25,101). A trace serum protein has been found in preliminary experiments to occur in approximately 60 percent of women with children, but not in men.

  The research program presented in this application will be devoted to the purification of the new protein from human serum, and to the chemical and physiochemical characterization of the isolated material.

  Purification and isolation will be achieved by conventional methods, such as ion exchange chromatography, gel filtration, ultracentrifugal sedimentation, zone electrophoresis and fractional precipitation. Immunodiffusion methods will be used as a specific qualitative and quantitative test for the trace component.

4.2.D Fractionation and Preservation--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

4.2.E Fractionation and Preservation--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

4.2.F Fractionation and Preservation--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

4.2.G Fractionation and Preservation--National Institute of General Medical Sciences

No identified ongoing NIGMS supported activities are related directly to this area.

4.2.H Fractionation and Preservation--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

4.2.I Fractionation and Preservation--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

4.2.J Fractionation and Preservation--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency --P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: PL 480 supported programs are listed in this volume under the appropriate sponsoring organization.

4.2.K Fractionation and Preservation--Bureau of Health Manpower Education

No identified ongoing BHME supported activities are related directly to this area.

4.2.L Fractionation and Preservation--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

4.2.M Fractionation and Preservation--Division of Research Resources

In FY 72, DRR supported one general clinical research center grant with one relevant component (FY 72: $15,433--%). The study addressed:

- Plasmapheresis as Treatment in Autoimmune Disease (Human).

In FY 72, DRR funded one general research support grant in the area of hematology (FY 72: $223,940). No further description was available at the time of report preparation.

See Section 4.1.M for general discussion of DRR activities.

4.3 LABORATORY PROCEDURES AND CONTROLS

4.3.A Laboratory Procedures and Controls--National Institute of Allergy and Infectious Diseases

Eight contracts, totalling $1,218,568, and 13 grants, totalling $468,237, were awarded by NIAID from 1972 funds for work on viral hepatitis. Major emphasis in the contract program is placed on a study of hepatitis B (serum hepatitis) since recent knowledge of hepatitis B antigen (known also as Australia antigen) has made it possible to define this disease. The long-range goal is development of a vaccine or other means of control. Animal model systems are being developed and a reference laboratory has been established. The latter serves as a resource for all NIH scientists working in the field of hepatitis.

In the grants area, NIAID supported scientists are attempting to isolate and characterize the causative agents of both hepatitis A (infectious hepatitis) and hepatitis B. Epidemiologic and immunologic studies are assessing the impact of viral hepatitis in various population groups. Three of these grant supported studies are broad in scope but include a definite segment of research on hepatitis. The role of Australia antigen and other agents in the development of serum hepatitis is being examined and better means of detecting these agents in the blood of potential donors are being sought.

4.3.B Laboratory Procedures and Controls--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported activities are related directly to this area.

4.3.C Laboratory Procedures and Controls--National Cancer Institute

In FY 72, NCI funded and administered one contract which is relevant to this area. No description of the scope of the contract was available.

- HL-A Typing for Platelet and Leukocyte Transfusions (FY 72: $246,606).

4.3.D Laboratory Procedures and Controls--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

4.3.E Laboratory Procedures and Controls--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

4.3.F Laboratory Procedures and Controls--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

4.3.G Laboratory Procedures and Controls--National Institute of General Medical Sciences

No identified ongoing NIGMS supported activities are related directly to this area.

4.3.H Laboratory Procedures and Controls--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

4.3.I Laboratory Procedures and Controls--National Institute of Neurological Diseases and Stroke

The NINDS funds and administers research related to this area (at the time this report was prepared, information as to funding mechanism and FY 72 funding levels was not available).

- Epidemiology of Cytomegalovirus Infection During Pregnancy and Repeat Abortions. The project is designed to determine, in a study of 2000 pregnant women:
  - When during the gestational period that cytomegalovirus infection is most critical to produce an abnormal outcome (i.e., a congenital abnormality)
  - Further information about the communicability of CMV to other members of the family from a congenitally infected infant.
- Chronic Infection with Cytomegalovirus as in Man and Animals. This project involves a study of chronic cytomegalovirus infection antibody levels, virus excretions, lymphocyte response in diseases of man and mice. The investigation relates specific

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pathologic processes to antibody levels and virus excretion patterns. Children with acute or chronic leukemia have been studied for approximately two years. Results indicate a correlation between clinical symptoms and rise in antibody titers to CMV.

- Transmission of Hepatitis B Agent to Subhuman Primates. The objective of this project is to establish an animal model to facilitate the study of the transmission and pathogenesis of the disease. To date, several species of nonhuman primates (Rhesus monkey, Cebus monkey, African green monkey, Patas monkey, Wooley monkey and Marmoset) have been inoculated with HB Ag-positive plasma. Evidence for serial transmission of an agent associated with HB Ag in the Rhesus monkey has been obtained; five serial passages have been completed and a pool of potentially infectious material prepared for further study. Infection of the Rhesus monkey was documented by the detection of a transient HB Ag antigenemia following an incubation period of 8-13 weeks and the subsequent development of anti-Hb antibody temporarily related to the antigenemia. However, none of the animals developed clinical or subclinical hepatitis. Nevertheless, the Institute feels that the Rhesus monkey should prove a valuable tool for the characterization of the agent of hepatitis B.

- Investigation of the Etiology and Effect of Serum and Infectious Hepatitis in the Perinatal Period. The project is designed to:

  - Determine the etiology of Australia antigen associated (serum) and infectious hepatitis

  - Determine the relationship of hepatitis/congenital jaundice and postnatal jaundice

  - Develop animal models and new diagnostic tests for these diseases.

  A large epidemic of infectious hepatitis (600 cases) occurred in a training school and hospital during the summer of 1970. These samples represent serial specimens obtained prior to the development of disease, at

time of acute disease and post infection. A 6- and 12-month follow-up has now been carried out. Australia antigen determinations were performed on 1200 patients. A controlled study of the effect of gamma globulin on this strain of infectious hepatitis was initiated. Serum and fecal samples will be cultured in a variety of tissue culture systems and inoculated into experimental animals.

Serum samples from patients with hepatitis and their immediate family are being collected and tested for Australia antigen and antibody to determine if Australia-associated hepatitis is spread by nonparenteral routes. Selected samples from the perinatal collaborative project are being tested for the presence of Australia antibody.

4.3.J Laboratory Procedures and Controls--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

4.3.K Laboratory Procedures and Controls--Bureau of Health Manpower Education

No identified ongoing BHME supported activities are related directly to this area.

4.3.L Laboratory Procedures and Controls--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

4.3.M Laboratory Procedures and Controls--Division of Research Resources

DDR supported two general clinical research center grants with two relevant components (FY 72: $40,780--%). These studies addressed:

- Detection of Occult Lung Disease in Blood Donors (human)
- Liver Disease in Australia Antigen Positive Blood Donors.

See Section 4.1.M for general description of DRR activities.

4.4 UTILIZATION

4.4.A Utilization--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

4.4.B Utilization--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area (FY 72: one grant, totalling $27,855):

- Biologic Bases of Nonhemolytic Transfusion Reactions. This research project is attempting to define additional antibodies to Ig A and Ig M in the hope of identifying allotypes of these proteins, to determine the mode of their inheritance and population polymorphism, and explore their clinical significance in transfusion reactions and isoimmunization in pregnancy. Efforts will be made to define the importance of these antibodies in transfusion reactions compared with antibodies to platelets and especially leukocytes which have been incriminated in the past for causation of febrile transfusion reactions.

4.4.C Utilization--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

4.4.D Utilization--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

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4.4.E Utilization--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

4.4.F Utilization--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

4.4.G Utilization--National Institute of General Medical Sciences

The NIGMS funds and administers a grant supported project related to this area (FY 72: one grant, totalling $238,420).

This project, Blood groups in nonhuman primates, has revealed that apes and monkeys possess homologues and analogues of the blood group systems of man (this realization provides a new tool for the study of human blood groups and human immunology and genetics). In more detail, studies performed in this project in 1971 dealt with, 1) new information on blood groups of nonhuman primates, 2) production and stockpiling of reagents (antisera) for simian-type blood factors; not only for those previously found and now standardized, but also for blood factors discovered in 1971, 3) functioning as the Reference Primate Blood Group Laboratory by assisting other investigators with blood typing of primates, and by providing training and blood grouping reagents.

In 1972 these studies continued for further elucidation of the primate animal homologues and analogues of the human

blood group systems. In addition, the production and stockpiling of new and previously found reagents as well as functioning as the Reference Primate Blood Group Laboratory has continued.

4.4.H Utilization--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

4.4.I Utilization--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

4.4.J Utilization--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

4.4.K Utilization--Bureau of Health Manpower Education

No identified ongoing BHME supported activities are related directly to this area.

4.4.L Utilization--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

4.4.M Utilization--Division of Research Resources

DRR supported three general clinical research center grants with three relevant components (FY 72: $60,567--%). These studies addressed:

- Plasma exchange in hepatic failure (human)
- Posttransfusional hepatitis (human)
- Hemodynamic changes in fast and slow exchange transfusion (human).

See Section 4.1.M for general description of DRR activities.

4.5 SYSTEMS MANAGEMENT

4.5.A Systems Management--National Institute of Allergy and Infectious Diseases

No identified ongoing NIAID supported research activities are related directly to this area.

4.5.B Systems Management--National Institute of Arthritis, Metabolism, and Digestive Diseases

No identified ongoing NIAMDD supported activities are related directly to this area.

4.5.C Systems Management--National Cancer Institute

No identified ongoing NCI supported research activities are related directly to this area.

4.5.D Systems Management--National Institute of Dental Research

No identified ongoing NIDR supported research activities are related directly to this area.

4.5.E Systems Management--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

4.5.F Systems Management--National Eye Institute

No identified ongoing NEI supported research activities are related directly to this area.

4.5.G Systems Management--National Institute of General Medical Sciences

No identified ongoing NIGMS supported activities are related directly to this area.

4.5.H Systems Management--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

4.5.I Systems Management--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

4.5.J Systems Management--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

4.5.K Systems Management--Bureau of Health Manpower Education

No identified ongoing BHME research activities are related directly to this area.

4.5.L Systems Management--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources
- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

4.5.M Systems Management--Division of Research Resources

No identified ongoing DRR supported research activities are related directly to this area.

4.6 TRANSPLANTATION

4.6.A Transplantation--National Institute of Allergy and Infectious Diseases

One of NIAID's major program areas is transplantation immunology. At present, 49 grants and 15 contracts support studies of the immune response as expressed in the rejection of organs and tissues transplanted from one individual to another. Approximately $6.7 million of 1972 funds are invested in grants and contracts in this area.

Six of NIAID's contracts support evaluation of tissue matching for transplantation, particularly between unrelated individuals. Other contracts provide a continuing supply of high-quality typing sera for research on organ transplants and support the development of new typing techniques and materials. In addition, contract supported research is evaluating potentially active immunosuppressive drugs and sera.

Several of the NIAID grants support basic biochemical research on the HL-A antigens--substances on the white cells which are the basis for tissue matching in transplants. Other grants have been awarded for wide-ranging investigations of immune mechanisms involved in acceptance or rejection of transplants. These mechanisms include both humoral antibody and the cellular response. Bone marrow transplants and the serious problem of graft-versus-host disease following such operations are of special concern to a number of investigators.

NIAID supported scientists are also studying various means of suppressing the immune response or of inducing tolerance to a transplant. One team of investigators is focusing on the immunobiology of tissue transplantation and pregnancy under the assumption that if more were known about why the mother does not "reject" the fetus for nine months, this knowledge might be put to work to the benefit of the transplant patient.

Much of the NIAID supported basic research in transplantation immunology may eventually be applicable to the control of cancer. At present, it is carried out in animals, ranging from mice to monkeys and including such species as sharks, turtles, and rabbits. Some investigations involve scientific engineering of the most sophisticated caliber. For example, immunobiological studies of cultured human lymphocytes may lead to the isolation and production of major HL-A antigens and antibodies, which could add new dimensions to control of immunological barriers.

4.6.B Transplantation--National Institute of Arthritis, Metabolism, and Digestive Diseases

The NIAMDD funds and administers research related to this area (FY 72: 32 grants, totalling $2,107,854--%; one contract, totalling $46,992).

Among the NIAMDD supported investigations related to this area are the following:

- Autoimmunity and Transplantation Immunology (FY 72: $87,106). One objective of this research project is the achievement of a harmless biological means of inducing in a potential homograft recipient a state of specific, selective, immunological unresponsiveness to the transplantation antigens of donor tissue.

- Organ Survival Under Experimental Conditions (FY 72: $58,312). The purpose of this research project is to improve the transplant procedures for the liver, pancreas, and intestine--and to find new means to enhance short-term, 12-24 hour, preservation. These latter efforts are concentrated on treatment of the donor, before organ removal and short-term, or continuous, perfusion with drugs. Also, the project is involved in the development of methods of utilizing implantable telemetry devices for evaluating surgical procedures and preservation methods for transplanted organs.

- Multidiscipline Study of Organ Transplantation (FY 72: $76,867). This research project involves studies related to whole organ preservation. Intact organs are removed from experimental animals and perfused with various solutions under investigation. The effects of alpha blockers (phenoxybenzamine), electrolyte composition of the perfusate and duration of cold ischemic time are being evaluated from the standpoint of survival following transplantation, release of lysosomal enzymes, hepatic cellular integrity, and reticuloendothelial integrity.

- Histocompatibility Antigens on Tissue Cells (FY 72: $28,596). The goal of this project is to determine whether there are isoantigens on the cells of human organs which are not shared with peripheral blood leukocytes, which may lead to antibody formation and which may play a role in the rejection of homografts. (If such isoantigens exist, it may be very important to type tissue cells directly before selecting a donor-recipient combination for organ transplantation. This would require the characterization of the antibody specificities in sera, collection and storage of adequate amounts of typing sera, and storage of well phenotyped cells to employ as a panel in the characterization of new sera.)

- Effect of Immunosuppressive Antisera on Hematopoiesis (FY 72: $26,455). This project is designed to explore the effects of antilymphocyte sera on hematopoiesis and to identify the areas of injury to marrow kinetics inflicted by such injury. Following documentation of the pattern of injury, attempts will be made to remove some of the irrelevant antibodies while retaining a significant portion of the immunosuppressive ability.

- Blood Grouping Studies in Primates (FY 72: $28,605). The overall objective of this research project is to contribute to the more effective use of nonhuman primates in the experimental study of transfusion reactions, erythroblastosis fetalis, tissue transplantation and induction of tolerance. To this end the determination of the number, distribution and genetic control of erythrocyte and leukocyte antigens of the genus Macaca has been investigated.

  Seven antisera detecting different erythrocyte factors have been prepared. Family studies to determine inheritance of these factors were instituted two years ago. Monkeys in the study included 135 infants born in the colony and both parents (15 males and 88 females) of each infant. A statistical and genetic analysis of the results is in progress.

  The initial phase of the experimental induction of tolerance to erythrocyte antigens is near completion. With the development of leukocyte typing serums, selection of donors and recipients for future experiments will be based upon leukocyte as well as erythrocyte types.

  Typing of the Celebes ape colony, begun in 1964, is being reactivated and family studies completed. A relationship between erythrocyte antigens and Macaca mulatta and Macaca niger seem to exist. The nature of this relationship is being explored.

- Clinical Homotransplantation of Tissues and Organs (FY 72: $7,669). The long-term goal of the proposed program is to overcome the problem of immunologic rejection of therapeutic tissue and organ transplants in patients. Thus far this program has pertained almost entirely to renal transplantation. The main research aims are to:

- Apply advances in basic immunogenetics research to therapeutic tissue and organ transplantation in patients

- Improve thereby the success rate of such treatment

- Utilize materials and information derived from patients to contribute to further immunogenetic advances.

Emphasis presently is on utilizing leukocyte typing and other methods of histocompatibility testing and developing these methods to their full potential of clinical usefulness in the selection of compatible donors. Further advances in histocompatibility testing and in immunosuppression may lead to practical means of establishing specific immunologic tolerance in man, which in some respects might be regarded the ultimate and ideal means of avoiding immunologic rejection.

4.6.C Transplantation--National Cancer Institute

In FY 72, NCI funded and administered five research grants, four program project grants and three contracts in this area. Among this research are the following projects:

- Immunology of Cancer (FY 72: $73,080). Humoral and cell-mediated immune responses of inbred mice to histocompatibility alloantigens are being assayed under conditions of active and passive immunization. Responses are being determined to the simultaneous injection of antigen and alloantiserum in different dosage ratios. Cell-mediated responses will be assayed by graft rejection or enhancement, by the graft-versus-host reaction, and by cell transfer to lethally irradiated mice.

  The immunoglobulin fractions of alloantiserums will be assayed for their activities in graft rejection and enhancement.

Immunosuppression will be studied for alloantiserums ("alloantilymphocyte" serums) directed against the animal being immunized. Responses to soluble and particulate heteroantigens and to histocompatibility alloantigens will be determined with respect to various antiserum dosage schedules and the genetic background of the animal.

- Transplantation Disease and Leukemia (FY 72: $92,890). An experimental model to test the hypothesis that autoreactive immunocytes can trigger the development of immunologic and neoplastic disease has been devised. Its basis is the graft-versus-host reaction induced in hybrid mice by parental strain spleen cells. When appropriate donors and hosts are selected, immune complex-mediated glomerulonephritis and malignant lymphomas develop. Before the appearance of these lesions, murine leukemia viruses are activated. These findings led to the concept that an immune response, especially of the type represented by the graft-versus-host reaction, can activate leukemia viruses. This idea is being tested by both *in vivo* and *in vitro* techniques. Whether or not immunosuppression plays any role in the activation of these viruses is also being studied. Preliminary evidence suggests that new antigens may appear on cells engaged in an immune response, perhaps because they are de-repressed. The notion that these neoantigens contribute to the sustained hyperplasia and ultimate neoplastic transformation of lymphoid tissue will be tested. Finally, parallel experiments indicate that a transmissible agent is present in canine systemic lupus. This agent may have the potential of inducing both autoimmunity and malignancy in mice. Further studies along these lines will be pursued.

- Studies of Marrow Transplantation, Intensive Chemotherapy, Extracorporeal Irradiation, Enzyme Therapy and Immunotherapy (FY 72: $70,725). The techniques involved are themselves an object of research involving ultraisolation techniques, gut sterilization, granulocyte transfusion, platelet transfusion, marrow storage and assessment of the patient's immunologic capability. The supporting laboratories provide critical information in the areas of molecular biology and histocompatibility typing. Data collection and processing is designed to provide maximum availability and utilization of the information generated in these studies.

- Implementation of Bone Marrow Transplantation (human) (FY 72: $23,876--%).
- Bone Marrow Transplantation Studies in Rhesus Monkeys (FY 72: $301,025).
- Isolation and Characterization of Transplantation Antigens (FY 72: $115,400).
- Humoral and Cell-Bound Antibody in Homografts (Rabbits, Mice, Rats), (FY 72: $7,000--%).

4.6.D Transplantation--National Institute of Dental Research

The NIDR funds and administers research related to this area (FY 72: four grants, totalling $207,000).

Among the NIDR supported research in this area are the following investigations:

- Autogenous red marrow and cancellous bone implants
- Immunological mechanisms
- Dental research transplantation genetics
- Tissue compatibility and properties of biomaterials.

No project descriptions were available at the time this volume was prepared.

4.6.E Transplantation--National Institute of Environmental Health Sciences

No identified ongoing NIEHS supported research activities are related directly to this area.

4.6.F Transplantation--National Eye Institute

The NEI funds and administers grant research related to this area (FY 72: $347,000--%).

Among these research projects are the following:

- Effect of Preoperative Corneal Vascularization on Homograft Reaction (FY 72: $15,288). This study is one component of an NEI funded program project "Immunological Diseases of the Eye," and focuses upon corneal graft reactions and fundamental investigations on the role of antibody producing cells in the uvea, the limbus and the cornea.

- Suppression of Corneal Graft Reaction--Pretreatment (FY 72: $15,288). This study is one component of the NEI funded program project "Immunological Diseases of the Eye." No project description was available at the time this volume was prepared.

- Corneal Preservation (FY 72: $31,715). This research project, conducted at an NEI funded External Ocular Disease Center, includes an investigation of virus chemotherapy, corneal preservation, and the suppression of immune reactions.

4.6.G Transplantation--National Institute of General Medical Sciences

The NIGMS funds and administers research related to transplantation (FY 72: 14 grants, totalling $676,927--%).

Among the NIGMS research in this area are the following investigations:

- Studies of Aortic Valve Grafts (Dogs, Sheep, Human) (FY 72: $5,505--%). This study is part of an NIGMS Cellular and Molecular Pathology Program Project, whose central theme is the study of response of cells to injury with particular emphasis on the processes occurring at the subcellular and molecular levels. Several different aspects of the cell response to injury relevant to the problems involved in trauma and repair are being investigated. Among these are the healing process as it occurs in arteries and connective tissues; the formation and structure of connective tissue proteins including collagen, elastin and the glycoproteins, which provide the tensile strength for the tissues; effects of age, genetic, and metabolic factors, on fibroblast proliferation; factors involved in the production of myocardial cell injury in trauma; effects of drugs and anesthetic agents on the liver; and the role of antibodies to tissue constituents in relation to trauma and to transplantation.

- A Study of Myocardial Imaging in Heart Transplants (FY 72: $12,533--%). This study is one of a number of projects conducted within an NIGMS Pharmacology-Toxicology Center whose total programs are concerned with four major areas of investigations of drugs in man, with supporting animal research. These areas are: quantitative methodology in human pharmacology, drug metabolism and the effect of drugs on the endocrine--metabolic processes, effects of drugs in special states, including patients bearing organ transplants and patients in the pediatric age group, and adverse reactions to drugs.

- Preservation of Organs by Freezing (FY 72: $35,226--%). This NIGMS supported study, conducted by the American National Red Cross, leads ultimately to the preservation of organs by freezing. It is divided into two general portions, basic studies of the mechanism of freezing and the application of new and existing knowledge to the prevention of injury. The basic studies are directed at the question, how does osmotic dehydration alter membrane permeability? Known situations where permeability is reversibly altered are being studied to determine both the mechanism and how irreversible changes can artificially be made reversible. These studies utilize human red cells and platelets, mouse myocardial cells, Chinese hamster cells and frog muscle.

Research methods emphasize membrane studies using microelectrode and micropipette procedures, effects of pressure loss of lipid and protein during hypertonic stress and repair or replacement of their loss, alteration of membrane permeability with chemical agents and study of the effect of stabilizing agents on resistance to osmotic stress. Studies of the prevention of freezing injury center on means of utilizing the reversible leak of solute across the cell membrane to reduce the amount of penetrating cryoprotectant required, means of increasing cell resistance to osmotic stress and a search for new cryoprotectants. As promising procedures are demonstrated on single cells and tissues, they will be tested on rat and rabbit hearts under perfusion.

- A Study of Genetic Aspects of Tissue Transplantation (FY 72: $32,789). A state of immunological tolerance, or specific unresponsiveness to a foreign antigen, may be induced in amphibians (leopard frogs) by either joining two nonsibling embryos in parabiotic union or by allotransplanting massive doses of embryonic tissue (neural fold). This program is aimed at elucidating the mechanism of induction and maintenance (or breakdown) of tolerance toward tissue antigens. The working hypothesis is that the state of nonreactivity to a particular antigen arises by the deletion of the clone, or clones, of competent lymphocytes capable of responding to the antigen. The implication is that a tolerant cell as an entity does not exist. The waning of tolerance occurs through the emergence of a new population of uninhibited cells. The breakdown of artificially induced tolerance may be partly mediated by the thymus, which may influence the differentiation of the newly arisen antigen-reactive cells. Accordingly, several experiments relate the thymus to the phenomenon of tolerance.

4.6.H Transplantation--National Institute of Child Health and Human Development

No identified ongoing NICHD supported research activities are related directly to this area.

NHLI

4.6.I Transplantation--National Institute of Neurological Diseases and Stroke

No identified ongoing NINDS supported research activities are related directly to this area.

4.6.J Transplantation--Fogarty International Center

The Fogarty International Center for Advanced Study in the Health Sciences serves as the focal point for the international activities of the National Institutes of Health. It is responsible for the administration of Scientific Activities Overseas (including the NIH Special Foreign Currency--P.L. 480--Program), Conferences and Seminars, International Fellowships, and Scholars in Residence Programs. Note: P.L. 480 supported programs are listed in this volume under the appropriate sponsoring organization.

4.6.K Transplantation--Bureau of Health Manpower Education

No identified ongoing BHME supported manpower activities are related directly to this area.

4.6.L Transplantation--National Library of Medicine

NLM supports two major types of activities which apply, in part, to the interests, activities and goals of NHLI:

- Publications and information retrieval related to cardiovascular, pulmonary and blood diseases and blood resources

- Biomedical communications systems which assist in the training of health personnel. NLM's Lister Hill Center applies communications and computer technology to the improvement of health care delivery, medical education, and biomedical research.

4.6.M Transplantation--Division of Research Resources

DRR supported three biotechnology resources grants with three relevant components (FY 72: $22,864--%). These studies addressed:

- Tissue typing
- Kidney transplantation
- Control for artificial heart (dogs).

DRR supported 22 general clinical research center grants with 29 relevant components (FY 72: $493,012--%). The subject of these studies included:

- Heart transplantation
- Kidney transplantation
- Lung transplantation
- Valve and blood vessel transplantation
- Skin transplantation
- Tissue compatibility
- Immunosuppression
- Tissue donors.

See Section 4.1.M for general description of DRR activities.

APPENDIX

NHLI

APPENDIX

This appendix is presented in two parts:

- Activities Index by NIH Components (Part A.1)
- Summary Program Support Data (Part A.2)

A.1 ACTIVITIES INDEX BY NIH COMPONENTS

Listed in the following paragraphs, on an NIH organizational component basis, are the problem areas (with section numbers for reference) related to which each NIH component conducts or sponsors research activities related to the National Heart, Blood Vessel, Lung and Blood Program.

- National Institute of Allergy and Infectious Diseases (NIAID)
  - Congenital Heart Disease (Section 1.6.A)
  - Rheumatic and Other Valvular Heart Diseases (Section 1.7.A)
  - The Normal Lung (Section 2.1.A)
  - Environmental Respiratory Diseases (Section 2.2.A)
  - Emphysema and Chronic Bronchitis (Section 2.3.A)
  - Allergic Airway Diseases--Asthma (Section 2.5.A)
  - Infectious Respiratory Diseases (Section 2.7.A)
  - Sarcoid and Gramulomatous Lung Diseases (Section 2.8.A)
  - Hypersensitivity Lung Diseases (Section 2.9.A)
  - Cystic Fibrosis (Section 2.12.A)
  - Hemophilia and Other Bleeding Disorders (Section 3.1.A)
  - Disorders of Hemostasis Due to Platelet Abnormalities (Section 3.3.A)
  - Laboratory Procedures and Controls (Section 4.3.A)
  - Transplantation (Section 4.6.A)

- National Institute of Arthritis, Metabolism and Digestive Diseases (NIAMDD)
  - Atherosclerosis (Section 1.1.B)
  - Hypertension (Section 1.4.B)
  - Cardiomyopathy (Section 1.8.B)
  - The Normal Lung (Section 2.1.B)
  - Infectious Respiratory Diseases (Section 2.7.B)
  - Hyaline Membrane Disease of the Newborn (Section 2.11.B)
  - Cystic Fibrosis (Section 2.12.B)
  - Hemophilia and Other Bleeding Disorders (Section 3.1.B)
  - Arterial Thromboembolism (Section 3.2.B)
  - Disorders of Hemostasis Due to Platelet Abnormalities (Section 3.3.B)
  - Venous Thrombosis and Pulmonary Embolism (Section 3.4.B)
  - Thromboembolism in Relation to Prosthetic Devices (Section 3.5.B)
  - Hemoglobinopathies (Section 3.7.B)
  - Fractionation and Preservation (Section 4.2.B)
  - Utilization (Section 4.4.B)
  - Transplantation (Section 4.6.B)
- National Cancer Institute (NCI)
  - The Normal Lung (Section 2.1.C)
  - Environmental Respiratory Diseases (Section 2.2.C)
  - Sarcoid and Granulomatous Lung Diseases (Section 2.8.C)

- Extrapulmonary Manifestations of Respiratory Diseases (Section 2.14.C)
- Arterial Thromboembolism (Section 3.2.C)
- Disorders of Hemostasis Due to Platelet Abnormalities (Section 3.3.C)
- Venous Thrombosis and Pulmonary Embolism (Section 3.4.C)
- Microcirculatory Thrombosis (Section 3.6.C)
- Hemoglobinopathies (Section 3.7.C)
- Blood Collection (Section 4.1.C)
- Fractionation and Preservation (Section 4.2.C)
- Laboratory Procedures and Controls (Section 4.3.C)
- Transplantation (Section 4.6.C)

• National Institute of Dental Research (NIDR)

- Atherosclerosis (Section 1.1.D)
- Coronary Heart Disease (Section 1.2.D)
- Peripheral Vascular Disease (Section 1.3.D)
- Congenital Heart Disease (Section 1.6.D)
- Cardiac Failure (Section 1.10.D)
- The Normal Lung (Section 2.1.D)
- Microcirculatory Thrombosis (Section 3.6.D)
- Transplantation (Section 4.6.D)

• National Institute of Environmental Health Services (NIEHS)

- Atherosclerosis (Section 1.1.E)
- Coronary Heart Disease (Section 1.2.E)
- Hypertension (Section 1.4.E)

- Congenital Heart Disease (Section 1.6.E)
- The Normal Lung (Section 2.1.E)
- Environmental Respiratory Diseases (Section 2.2.E)
- Emphysema and Chronic Bronchitis (Section 2.3.E)
- Allergic Airway Diseases--Asthma (Section 2.5.E)
- Infectious Respiratory Diseases (Section 2.7.E)
- Hemoglobinopathies (Section 3.7.E)

• National Eye Institute (NEI)

- Atherosclerosis (Section 1.1.F)
- Hypertension (Section 1.4.F)
- Stroke (Section 1.5.F)
- Shock (Section 1.11.F)
- Microcirculatory Thrombosis (Section 3.6.F)
- Hemoglobinopathies (Section 3.7.F)
- Transplantation (Section 4.6.F)

• National Institute of General Medical Sciences (NIGMS)

- Atherosclerosis (Section 1.1.G)
- Coronary Heart Disease (Section 1.2.G)
- Peripheral Vascular Disease (Section 1.3.G)
- Hypertension (Section 1.4.G)
- Stroke (Section 1.5.G)
- Congenital Heart Disease (Section 1.6.G)
- Cardiomyopathy (Section 1.8.G)
- Arrhythmia (Section 1.9.G)

- Cardiac Failure (Section 1.10.G)
- Shock (Section 1.11.G)
- The Normal Lung (Section 2.1.G)
- Emphysema and Chronic Bronchitis (Section 2.3.G)
- Pulmonary Vascular Diseases (Section 2.10.G)
- Hyaline Membrane Disease of the Newborn (Section 2.11.G)
- Acute and Chronic Respiratory Failure (Section 2.13.G)
- Hemophilia and Other Bleeding Disorders (Section 3.1.G)
- Arterial Thromboembolism (Section 3.2.G)
- Disorders of Hemostasis Due to Platelet Abnormalities (Section 3.3.G)
- Venous Thrombosis and Pulmonary Embolism (Section 3.4.G)
- Thromboembolism in Relation to Prosthetic Devices (Section 3.5.G)
- Microcirculatory Thrombosis (Section 3.6.G)
- Hemoglobinopathies (Section 3.7.G)
- Utilization (Section 4.4.G)
- Transplantation (Section 4.6.G)

• National Institute of Child Health and Human Development (NICHD)

- Atherosclerosis (Section 1.1.H)
- Hypertension (Section 1.4.H)
- Stroke (Section 1.5.H)
- Congenital Heart Disease (Section 1.6.H)

- Arrhythmia (Section 1.9.H)
- Shock (Section 1.11.H)
- The Normal Lung (Section 2.1.H)
- Pediatric Obstructive Respiratory Diseases (Section 2.4.H)
- Allergic Airway Diseases--Asthma (Section 2.5.H)
- Pulmonary Vascular Diseases (Section 2.10.H)
- Hyaline Membrane Disease of the Newborn (Section 2.11.H)
- Disorders of Hemostasis Due to Platelet Abnormalities (Section 3.3.H)
- Hemoglobinopathies (Section 3.7.H)

• National Institute of Neurological Diseases and Stroke (NINDS)

- Hypertension (Section 1.4.I)
- Stroke (Section 1.5.I)
- Congenital Heart Disease (Section 1.6.I)
- Arrhythmia (Section 1.9.I)
- Pulmonary Vascular Diseases (Section 2.10.I)
- Disorders of Hemostasis Due to Platelet Abnormalities (Section 3.3.I)
- Laboratory Procedures and Controls (Section 4.3.I)

• Bureau of Health Manpower Education (BHME)

- Coronary Heart Disease (Section 1.2.K)
- Peripheral Vascular Disease (Section 1.3.K)
- Hypertension (Section 1.4.K)
- Stroke (Section 1.5.K)

- Congenital Heart Disease (Section 1.6.K)
- Rheumatic and Other Valvular Heart Diseases (Section 1.7.K)
- Arrhythmia (Section 1.9.K)
- Cardiac Failure (Section 1.10.K)
- Shock (Section 1.11.K)
- Environmental Respiratory Diseases (Section 2.2.K)
- Emphysema and Chronic Bronchitis (Section 2.3.K)
- Pediatric Obstructive Respiratory Diseases (Section 2.4.K)
- Allergic Airway Diseases--Asthma (Section 2.5.K)
- Diffuse Interstitial Respiratory Diseases (Section 2.6.K)
- Infectious Respiratory Diseases (Section 2.7.K)
- Hypersensitivity Lung Diseases (Section 2.9.K)
- Cystic Fibrosis (Section 2.12.K)
- Acute and Chronic Respiratory Failure (Section 2.13.K)
- Hemophilia and Other Bleeding Disorders (Section 3.1.K)
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- Venous Thrombosis and Pulmonary Embolism (Section 3.4.K)
- Hemoglobinopathies (Section 3.7.K)
- Blood Collection (Section 4.1.K)

- National Library of Medicine (NLM)
  - Environmental Respiratory Diseases (Section 2.2.L)
  - Hemophilia and Other Bleeding Disorders (Section 3.1.L)
  - Microcirculatory Thrombosis (Section 3.6.L)
- Division of Research Resources (DRR)
  - Atherosclerosis (Section 1.1.M)
  - Coronary Heart Disease (Section 1.2.M)
  - Peripheral Vascular Disease (Section 1.3.M)
  - Hypertension (Section 1.4.M)
  - Stroke (Section 1.5.M)
  - Congenital Heart Disease (Section 1.6.M)
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- Microcirculatory Thrombosis (Section 3.6.M)
- Hemoglobinopathies (Section 3.7.M)
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- Laboratory Procedures and Controls (Section 4.3.M)
- Utilization (Section 4.4.M)
- Transplantation (Section 4.6.M)

A.2 SUMMARY PROGRAM SUPPORT DATA

Table 1 depicts the fiscal year 1972 (FY 72) funding level for identified related programs supported by 13 organizational components of the National Institutes of Health, exclusive of the National Heart and Lung Institute.

As depicted in Table 1:

- More than $50,000,000 in identified activities related to heart, blood vessel, lung and blood diseases and blood resources were supported by the 13 NIH components. This included:
  - Heart and Blood Vessel Diseases related activities in excess of $17,500,000
  - Lung Diseases related activities at more than $12,500,000
  - Blood Diseases related activities in excess of $6,800,000
  - Blood Resources related activities (including transplantation) at more than $12,900,000.
- Funding data was not available for some identified activities (indicated by an asterisk in Table 1).

TABLE 1

Related Program Funding--FY 72
(in Thousands of Dollars)

PROBLEM AREA	NIH COMPONENTS													PROBLEM AREA TOTAL
	NIAID	NIAMDD	NCI	NIDR	NIEHS	NEI	NIGMS	NICHD	NINDS	FIC	BHME	NLM	DRR	
ATHEROSCLEROSIS		1,586		296	259	26	66**	216					779	3,228
CORONARY HEART				163	38		442				95		568	1,306
PERIPHERAL VASCULAR				R			73				R		121	194
HYPERTENSION		550			40R	16R	51	52	268		R		1,964	2,941
STROKE						23R	97	146	5,306		96R		127	5,795
CONGENITAL HEART	44			17	164		324	432	*		R		478	1,459
RHEUMATIC HEART	239										R		328	567
CARDIOMYOPATHY		94					324						89	507
ARRHYTHMIA							179	50	* 105R		R		421	755
CARDIAC FAILURE				R			*				17R		222	239
SHOCK						50R	382*	52			R		34	518
SUBTOTAL	283	2,230		476	501	115	1,938	948	5,679		208		5,131	17,509
NORMAL LUNG	30	25	26	1,097	410		*	337*					249	2,174
ENVIRONMENTAL RESPIRATORY	44		R		965						R	*	32	1,041
EMPHYSEMA AND BRONCHITIS	175				R		10				546		168	899
PEDIATRIC RESPIRATORY								51			R		48	99
ASTHMA	675				44			53			R		146	918
INTERSTITIAL RESPIRATORY											R			
INFECTIOUS RESPIRATORY	863	120			93						R		46	1,122
SARCOID AND GRANULOMATOUS	30		R										15	45
HYPERSENSITIVITY	745										R		20	765
PULMONARY VASCULAR							4,300	30	**				135	4,465
HYALINE MEMBRANE		23					15R	432R					172	642
CYSTIC FIBROSIS	30	227									R		27	284
RESPIRATORY FAILURE							92				R		63	155
EXTRA-PULMONARY MANIFESTATIONS			63										11	74
SUBTOTAL	2,592	395	89	1,097	1,512		4,417	903			546		1,132	12,683
HEMOPHILIA	41	15					37				R	*	30	123
ARTERIAL THROMBOEMBOLISM		41	R				*				R		60	101
HEMOSTASIS DISORDERS	10	90	31				97	27	*		20		252	527
VENOUS THROMBOSIS		R	R				R				R		13	13
PROSTHETIC DEVICES		604					R						40	644
MICROCIRCULATORY THROMBOSIS			R	23		35	R					*	30	88
HEMOGLOBINOPATHIES		3,469	140		14	R	570**	82			R		1,095	5,370
SUBTOTAL	51	4,219	171	23	14	35	704	109			20		1,520	6,866
BLOOD COLLECTION			22								R			22
FRACTIONATION		62	555										239	856
LABORATORY PROCEDURES	169		247						*				41	457
UTILIZATION		28					238						61	327
SYSTEMS MANAGEMENT														
TRANSPLANTATION	6,700	2,155	684*	207		347	677						516	11,286
SUBTOTAL	6,869	2,245	1,508	207		347	915						857	12,948
AGENCY TOTAL	9,795	9,089	1,768	1,803	2,027	497	7,974	1,960	5,679		774		8,640	50,006

* = PROJECTS WERE SUPPORTED FOR WHICH FUNDING INFORMATION WAS NOT AVAILABLE

** = PROGRAM PROJECT TOTAL FUNDING WAS AVAILABLE; HOWEVER, ESTIMATES OF AMOUNT OF FUNDING RELATED SPECIFICALLY TO THE NATIONAL PROGRAM WERE NOT AVAILABLE. THEREFORE, TO AVOID OVERSTATEMENT OF RELATED PROGRAMS, FUNDS ARE NOT REPORTED IN THIS TABLE. SEE SECTIONS 1.1.G., 2.10.I, AND 3.7.G OF THIS REPORT

R = RELATED PROJECTS OF NIH COMPONENT ARE DISCUSSED IN A SECTION CROSS-REFERENCED IN THE TEXT

U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service
National Institutes of Health
National Heart and Lung Institute
DHEW Publication No. (NIH) 73–523

NATIONAL HEART, BLOOD VESSEL, LUNG AND BLOOD PROGRAM

VOLUME V
PROGRAM ANALYSIS

PART III

OTHER FEDERAL AGENCIES (USDA, AEC, DOD, EPA, FDA, HSMHA, NASA, NSF, SRS, SSA, DOT, AND VA)

MARCH 31, 1973

U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service
National Institutes of Health
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Public Health Service
National Institutes of Health
National Heart and Lung Institute
DHEW Publication No. (NIH) 73–524

For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402
Price $2.85 domestic postpaid or $2.50 GPO Bookstore

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P R E F A C E

Volume V, Program Analysis, is a compilation of program information describing federally supported research efforts relevant to heart, blood vessel, lung and blood diseases and blood resources. The information presented is based on data from fiscal year 1972 (FY 72), the most recent period for which detailed program data are available. An exception is the program (discussed in Part III) of the Environmental Protection Agency for which FY 73 figures are given, since that is the first full year of Agency operation.

Volume V, Program Analysis, is presented in three parts:

Part I - National Heart and Lung Institute

Part II - National Institutes of Health (exclusive of the National Heart and Lung Institute)

Part III - Other Federal Agencies, (USDA, AEC, DOD, EPA, FDA, HSMHA, NASA, NSF, SRS, SSA, DOT, and VA)

Volume V was prepared by the National Heart and Lung Institute with the support and cooperation of the members of the Interagency Technical Committee (IATC) and their respective organizations. The Interagency Technical Committee on Heart, Blood Vessel, Lung and Blood Diseases and Blood Resources is, by law, "responsible for coordinating those aspects of all federal health programs and activities relating to heart, blood vessel, lung and blood diseases and to blood resources to assure the adequacy and technical soundness of such programs and activities and to provide for the full communication and exchange of information necessary to maintain adequate coordination of such programs and activities."

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F O R E W O R D

This report is Part III of Volume V, Program Analysis, of the National Heart, Blood Vessel, Lung and Blood Program. Summarized herein are the activities related to heart, blood vessel, lung and blood diseases and blood resources supported by agencies which are members of the Interagency Technical Committee (IATC) exclusive of the National Institutes of Health. These agencies are:

- Department of Agriculture
- Atomic Energy Commission
- Department of Defense
- Environmental Protection Agency
- Food and Drug Administration
- Health Services and Mental Health Administration
- National Aeronautics and Space Administration
- National Science Foundation
- Social and Rehabilitation Service
- Social Security Administration
- Department of Transportation
- Veterans Administration.

The activities documented in this report are grouped into categories corresponding to the 39 major problem areas considered by the four advisory panels and their task groups in their contributions to the National Heart, Blood Vessel,

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Lung and Blood Progam. Within each category (e.g., Atherosclerosis), the activities conducted or sponsored by all agencies in fiscal year 1972 (FY 72)* are described.

Figure 1 summarizes the perspective from which each of the agencies supports activities related to the National Heart, Blood Vessel, Lung and Blood Program. In FY 72, the agencies sponsored related research at a level in excess of $81,000,000 (see Appendix).

This report is presented in four sections and an appendix:

- Heart and Blood Vessel Diseases--outlines activities in FY 72 of the twelve agencies related to eleven major problem areas (Section I).
- Lung Diseases--summarizes FY 72 activities related to fourteen major problem areas (Section II).
- Blood Diseases--discusses, in seven major problem areas, research efforts supported in FY 72 (Section III).
- Blood Resources--outlines activities in FY 72 supported in six major problem areas (Section IV).
- Appendix--provides an index correlating the efforts of the twelve agencies with the 39 problem areas and presents summary data on level of support (dollars) by agency and for each program area.

*Except for those of EPA which are for FY 73.

Figure 1

SUMMARY ACTIVITIES PERSPECTIVE - FEDERAL AGENCIES
(EXCLUDING NIH)

-USDA- The USDA funds and administers research concerned with nutrient composition of diet and effect of diet on pathogenesis of atherosclerosis, with blood diseases, and with the etiology of lung diseases linked with agricultural products.	-AEC- The AEC conducts relevant research dealing with the application of radiation and radioactive isotopes to the understanding of biological processes and to the treatment of heart and vascular disease. Work is also conducted in the application of advanced technology to problems of prosthetics, blood banking and transplantation.	DOD The DOD, via the research activities of the individual services (Army, Navy, Air Force) conducts relevant research, in anticipation of the potential incidence of heart and lung disease in service personnel, and the management of combat injuries involving these organs. Studies in blood banking and transplantation are also conducted.	-EPA- EPA conducts studies of environmental factors as related to the incidence of heart, blood and lung disease. Programs are directed at the effects of pesticides in the environment and the surveillance of communities to study the correlation of community health with varying levels and types of pollution.
-FDA- FDA conducts relevant work in the area of blood resources. Primary efforts are directed toward developing standards for laboratory processing of blood, with other efforts in blood fractionation and utilization. FDA's other relevant activity deals with the safety and efficacy of new drugs.	-HSMHA- Through its major operating components (e.g., RMPS, MCHS, NICHS, etc.), HSMHA funds and administers programs and activities related to prevention, detection and provision of health care services in the area of cardiovascular and pulmonary disease.	-NASA- NASA supports related mission oriented research directed at understanding, measuring and controlling body functions and mechanisms in diverse environmental states. Instrumentation and techniques have been and are being developed directly applicable to the cardiovascular and pulmonary systems.	-NSF- NSF supports research in biological processes fundamental to the understanding of cardiovascular and pulmonary disease. Also supported are special programs in biomedical engineering and technological applications.
-SRS- Relevant research supported by SRS is concerned with rehabilitation of patients who have suffered from cardiovascular and pulmonary disorders. Research is supported directly and through the payment of third party funds.	-SSA- The SSA supports no research in NHLI related areas; however, the SSA provides third party payments for the provision of care (which may involve participation in clinical research).	-DOT- DOT funds and administers, through NHTSA, research and development in Emergency Medical Services. The DOT also conducts, through its FAA, research focused on detection and prevention of incipient coronary heart disease.	-VA- The VA conducts research in most of National Plan problem areas. Projects are supported as part of intramural research and patient care activities in VA hospitals and clinics.

I. HEART AND BLOOD VESSEL DISEASES

I. HEART AND BLOOD VESSEL DISEASES

This section summarizes activities supported in FY 72* by the agencies represented on the Interagency Technical Committee (IATC) exclusive of the National Institutes of Health (NIH) in 11 categories:

- Atherosclerosis (1.1)
- Coronary Heart Disease (1.2)
- Peripheral Vascular Disease (1.3)
- Hypertension (1.4)
- Stroke (1.5)
- Congenital Heart Disease (1.6)
- Rheumatic and Other Valvular Heart Diseases (1.7)

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*An exception is the Environmental Protection Agency; since FY 73 is the first full year of EPA operations, FY 73 figures are presented.

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- Cardiomyopathy (1.8)
- Arrhythmia (1.9)
- Cardiac Failure (1.10)
- Shock (1.11).

1.1 ATHEROSCLEROSIS

1.1.A Atherosclerosis--Department of Agriculture (USDA)

Major objectives of research relating to atherosclerosis, conducted by the U. S. Department of Agriculture, concern the nutrient composition of the diet and the effect of diet on the pathogenesis of atherosclerosis.

While an explicit, per project FY 72 dollar figure was not provided, the USDA estimates their total effort in this area to be $1,040,000, with $1,000,000 of this expended in their intramural effort.

Among the USDA intramural projects related to this area are:

- Research on the Use of Ultrasound to Quantify Atherosclerotic Lesions. The USDA is working on a project quite similar to that funded and administered by the National Heart and Lung Institute (NHLI) Division of Technological Applications (See "Program Analysis: NHLI," Section 1.1.5, page 1-6).

  It is anticipated that the results of this investigation will be useful to supplement and complement diet studies designed to reduce blood lipids--by determining and measuring any regression of atherosclerotic lesions.

- USDA Surveys of Food Consumption. The USDA's Consumers Food Institute conducts nationwide food consumption surveys of households and individuals. These are conducted every 8-10 years (on a nationwide basis). At other periods the Institute conducts localized studies. The surveys serve as a basis for the determination of how much fat is getting into the diet from what commodities--and the effects of this on the population (stratified by age).

- Study on the Influx of Dietary Fat and Calcium on the Metabolism. The USDA funds and administers in its intramural program this study which relates to the effect of higher levels of calcium in the diet on the lowering of blood lipids. This study, which has followed a study of the effect of the level of protein intake on calcium requirement, is being conducted at present in animals--but will be extended to humans.

- Moderate Reduction of Blood Lipids by Dietary Means. The USDA funds and administers in its Lipid Nutrition Laboratory this study designed to reduce blood lipids through the substitution of diets high in polyunsaturated fatty acids for saturated fats. To date, decreases in blood lipids have been achieved by this means--but not to a sufficient enough degree. This study is attempting to test long-term diets containing less fat in healthy men and women in various decades of life. It is anticipated that this will result in the ability to predict the amount of meat, dairy products, and poultry that can be eaten to maintain serum cholesterol at 200 mg. % or less.

- Dietary Fat-Carbohydrate Interaction in Atherogenesis. The objective of this study is to clarify the interrelations between dietary P/S ratio, carbohydrate; fat ratio, concentration of serum lipids, and atherogenesis.

- Effect of Dietary Fat on the Lipid and Cholesterol Level in Blood, Liver, and Tissues of Rats. The objective of this study is to establish how sources of fat, sources of carbohydrate, and thyroid hormone influence blood and tissue lipids, tissue carbohydrate and enzyme levels in these tissues.

- Dietary Fats and Accumulations of Cholesterol and Glycerides in Tissues. The USDA funds and administers in its intramural program this study which has as its objective the determination of metabolic differences caused by dietary saturated and unsaturated fatty acids, dietary cholesterol and heredity that influence fat and cholesterol accumulation.

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- Increasing Polyunsaturated Fats in Milk and Meat of Ruminants. The objective of this research, conducted at the Agricultural Research Center, Beltsville, is to change the fat content and modify the fatty acid composition of dairy and animal products.

- Factors Affecting Serum Cholesterol Levels in Men. The objective of this research conducted at the Agricultural Research Center was to determine the relationship of selected gastrointestinal functions to serum cholesterol in men.

- Chemical and Physical Properties of Food Lipids Influencing Their Dietary Value. The objective of this research is to determine the triglyceride and phospholipid composition, structure and properties of food fats; to study the physical chemical properties of cholesterol and other lipids; to investigate the oxidative interaction of the tocopherols and fatty acids.

Among the USDA supported extramural research related to this area are the following projects:

- Nutritional Interrelationships in Lipid Metabolism. The objective of this research is to establish a rationale for recommending the polyunsaturated fat intake in relation to saturated fats, including hydrogenated fats. (This is a continuing effort at the University of Illinois.)

- Effect of Dietary Fat on Plasma Lipoproteins. The objective of this research is to determine how the type and quantity of dietary fat influence the state and metabolism of the cholesterol component of plasma lipoproteins. (This is a continuing effort at the University of Illinois.)

- Atherogenesis at the Cellular Level. The objective of this research is to determine the role of: arachidonate metabolism; oxidative metabolism; lipid accumulation; phosphatase activities; cell nutrition and age; and mucopolysaccharide metabolism in the transformation of aortic smooth muscle cells to foam cells. (This work is conducted at the University of New Hampshire.)

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- Dietary Carbohydrates and Lipid Metabolism in Humans. The USDA funds and administers a P.L. 480 study* at Hebrew University in Jerusalem, Israel. This study is designed to investigate dietary carbohydrate effects on human serum and tissue lipids and lipolytic enzymes. To date, subjects have been enrolled, questionnaire and data recording forms developed, and analytical methods established.

- Study of the Interaction of Dietary Fats and Carbohydrates. The USDA funds and administers a grant supported study (FY 72: one grant, totalling $29,500) of the interaction of dietary fats and carbohydrates in atherogenesis. The study is designed primarily to determine whether any excess calories from carbohydrates, when substituted for "fat calories" in the diet, have similar metabolic and atherogenetic properties as the result of *in vivo* synthesis of fat from the excess carbohydrate.

- Dietary Carbohydrates and Vascular Lesions. The USDA funds and administers a P.L. 480 study* at Hadassah Medical School in Jerusalem, Israel. This study has developed and partially defined a model system for studying the effects of dietary sucrose on degenerative disease. The high carbohydrate diet and the strain of rat used are such that feeding sucrose in place of starch resulted in lesions of the eyes and kidneys after 8-16 months of treatment. The kidneys became enlarged with characteristic signs of diffuse glomerulosclerosis. Eye lesions included a loss of microaneurysms in retinal capillaries. The abnormalities appeared to be vascular lesions.

*This refers to collaborative health research and research-related projects abroad which are supported entirely by foreign currencies owned by the U.S. which have been determined by the U.S. Treasury to be in excess of normal U.S. needs in the countries. The program helps achieve the domestic health objectives of DHEW and promotes U.S. foreign policy.

- Utilization of Dietary Fat from Various Sources. The objective of this research is to provide basic information for improved recommendations concerning kind and amount of fat in the human diet; specifically, relationships between lipid utilization and physiological state, normal and abnormal. (This is a seven-year program at Clemson University.)

- Inheritance of Atherosclerosis in Turkeys. The objectives of this study are: to establish two lines of turkeys that differ in the degree of atherosclerosis; after establishment of the lines--to study the mode on inheritance through reciprocal crosses; and to measure physiologically and biochemically changes that occur within the high and low incidence lines.

- Nutritional Interrelationships in Lipid Metabolism. The objectives of this research are to provide basic information for improved recommendations concerning kind and amount of fat in the human diet; specifically, relationships between dietary factors and lipids in blood and other tissues, relationships between lipids and other substances in metabolism, relationships between lipid utilization and physiological state, normal and abnormal.

- Nutritional Interrelationships in Lipid Metabolism. The objectives of this research are to provide basic information for improved recommendations concerning kind and amount of fat in the human diet; specifically, relationships between dietary factors and lipids in blood and other tissues, relationships between lipids and other substances in metabolism, relationships between lipid utilization and physiological state, normal and abnormal. (This is a five-year program at Kansas State University.)

- Nutritional Interrelationships in Lipid Metabolism. The objectives of this research are to provide basic information for improved recommendations concerning kind and amount of fat in the human diet; specifically,

relationships between dietary factors and lipids in blood and other tissues and relationships between lipids and other substances in metabolism. (This is a five-year program at Purdue University.)

- Laying Hen Diet and Cholesterol. The objective of this research is to determine the effects of dietary ingredients on level of cholesterol and/or cholesterol esters in egg yolk, blood serum, liver and other tissues. (This is a three-year program at the University of Delaware.)

- Lipid Studies of Atherosclerosis in Various Species of Animals. The objective of this research is to determine factors and their mechanisms operative in resistance or susceptibility to atherosclerosis with emphasis on the role of lipid metabolism. (This is a three-year program at the University of Hawaii.)

1.1.B Atherosclerosis--Atomic Energy Commission (AEC)

The AEC funds and administers contract supported studies in the area of atherosclerosis (FY 72: five onsite contracts, totalling $500,000).

- Research in three major AEC laboratories (Lawrence Berkeley Laboratory, Lawrence Livermore Laboratory, and the Franklin McLean Memorial Research Institute) is directed toward the study of the biochemistry and function of plasma lipoproteins. A variety of physical, chemical, and biological techniques is being utilized to elucidate lipoprotein structure and define structure-function relationships. Both lipid and protein moieties, as well as lipid-protein interactions, are being characterized. Enzymes involved in the formation and modification of plasma lipoproteins are under investigation. Progress is being

made in clarifying mechanisms by which complex lipoproteins are fabricated in the living organism. Other research is concerned with changes in plasma lipoprotein metabolism in disease states and effects of environmental factors on the distribution of lipoproteins in blood plasma. The research on plasma lipoproteins conducted at the Lawrence Berkeley Laboratory is also supported by three research grants from NHLI (FY 72: three grants, totalling $111,000).

- At the Brookhaven National Laboratory, both radioactive and stable (heavy) isotopes are being studied as agents for the early detection of metabolic abnormalities (such as those characteristic of diabetes or obesity) that may predispose an individual to atherosclerosis. Scientists at the Los Alamos Scientific Laboratory are also participating in the research dealing with stable isotopes.

As discussed under Section 2.2.B (Environmental Respiratory Diseases), investigators at the Oak Ridge National Laboratory (Analytical Chemistry Division) are currently conducting a detailed analysis of cigarette smoke under NCI support. AEC supported research on nuclear medicine technology, as discussed in Section 1.2.B (Coronary Heart Disease) is also pertinent to atherosclerosis.

1.1.C Atherosclerosis--Department of Defense (DOD)

For description of related research activities supported by the Department of the Air Force, see Section 1.3.C.

1.1.D Atherosclerosis--Environmental Protection Agency (EPA)

No identified ongoing EPA research is directly concerned with this area.

1.1.E Atherosclerosis--Food and Drug Administration (FDA)

No identified ongoing FDA supported research activities are related to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

1.1.F Atherosclerosis--Health Services and Mental Health Administration (HSMHA)

The Regional Medical Programs Services (RMPS), HSMHA, is supporting revision of guidelines for "Primary Prevention of Atherosclerotic Diseases" by the Intersociety Commission for Heart Disease (ICHD) Resources which were published in Circulation pp.A-55-95, December, 1970. The ICHD is supported by a contract from the RMPS to the American Heart Association through April 30, 1975, at a level of approximately $180,000 per year to update this and other guidelines.

1.1.G Atherosclerosis--National Aeronautic and Space Administration (NASA)

No identified ongoing NASA supported activities are related directly to this area.

1.1.H Atherosclerosis--National Science Foundation (NSF)

In FY 72 the NSF funded and administered five programs (FY 72 funding: $104,200) directed at measuring and modelling the flow of blood through healthy and obstructed blood vessels.

- Noninvasive Measurement of Physiological Flow Parameters. A research program in biomechanics is being carried out toward measuring, describing and interpreting various cardiovascular flow parameters in experimental animals under controlled conditions. Specific goals of this research are:

  - To obtain the capability to measure in vivo blood flow velocity, flow profiles and vessel geometry in arteries and veins using a pulsed ultrasound Doppler flowmeter

  - To evaluate the pulsed Doppler flowmeter for noninvasive measurements of blood velocity

  - To utilize the pulsed Doppler device in studies of coronary blood flow characteristics and venous hemodynamics in experimental animals.

  An integral part of the proposed research is a cooperative program with NASA's Ames Research Center which will provide access to current methods and future advances in pulsed ultrasound Doppler flowmeter technology and instrumentation as available from the Ames Research Center (applicable also to coronary heart disease and peripheral vascular disease).

- Effects of Localized Abnormalities on Blood Flow in Arteries. The objective of the proposed research is to analyze fluid dynamically blood flow in arteries with localized abnormalities to determine the effects of these abnormalities on the pressure and velocity waves. Two types of abnormalities are being considered: false aneurysm (balloon-like structures) which is being characterized as extremely distensible segments of the artery; and multiple atherosclerotic plaques with calcification, characterized as rigid tubes.

  Several mathematical techniques are being used to analyze the fluid dynamics of the problem. One- and two-dimensional linear formulations will be undertaken because results can be obtained rigorously. However, the complexity of the flow pattern demands that nonlinear analyses, both one- and two-dimensional, be pursued, necessitating numerical work by computer,

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which will provide more complete information about the effect of the abnormalities on the blood flow within the diseased vessel.

Experimental data is to be gathered by a pulsed ultrasound Doppler velocity detector for comparison with the mathematical models. Measurements are to be taken noninvasively in humans at Methodist hospital in Houston during the second summer. The waveforms will be analyzed considering the condition of the vessel being measured and will be compared with theoretical predictions. Different wall conditions will certainly produce significantly different waveforms so that eventually analysis of the waveform alone will provide diagnostic information about the condition of the blood vessel (applicable also to peripheral vascular disease).

- Pulsating Flow Through Rigid and Flexible Stenoses. Both steady and pulsatile flow through simulated vascular stenoses are being studied in order to compare the pertinent flow characteristics to the geometry and flexibility of the stenoses. Experimental results will be compared with a theoretical solution in order to assess the merits of the experimental techniques. Whole blood will then be used, and the pressures and separated regions determined and compared to those of the transparent fluid. Regions of relatively high and low pressure and wall shearing stress will be located. Flexible models will be constructed to some of the same geometries as the rigid tubes and the experimental results obtained will be compared to the previous cases. Finally, flow through mammalian arterial and/or venous segments will be studied and the results compared to the model studies (applicable also to peripheral vascular disease).

- Fluid Mechanics Problems in Arterial Disease. The effect of flow pulsations in a pipe on the nature of the flow and on the diffusive transport of high Schmidt number species is being studied under a laboratory flow system in vivo experiments, and related theoretical calculations. Hot film anemometer velocity profile measurements will be carried out and through frequency analysis, power spectrum obtained

for a range of conditions simulating arterial flow. Diffusive flux measurements will be carried out for similar conditions using radioactive tracer technologies. These results will be used to assess the importance of fluid mechanical aspects in the development of arterial disease (applicable also to coronary heart disease and peripheral vascular disease).

- Finite Deformation Waves in Arteries. The objective of this project is to establish nonlinear mathematical models and computer algorithms to describe the mechanical properties of arteries and their response to pulsatile and other dynamic loads. Detailed computations are being carried out assuming a nonlinear viscoelastic arterial wall with an instantaneous elastic response and the arterial pulse is mathematically described as a second-order singular surface. Experiments will be performed on animals to check the validity of the analytical models.

1.1.I Atherosclerosis--Social and Rehabilitation Services (SRS)

The SRS provides third party payments for provision of care (which may involve participation in clinical research).

1.1.J Atherosclerosis--Social Security Administration (SSA)

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

1.1.K Atherosclerosis--Department of Transportation (DOT)

No identified ongoing DOT supported activities related directly to this area.

1.1.L Atherosclerosis--Veterans Administration (VA)

The VA funds, conducts and administers numerous studies related to atherosclerosis. The following paragraphs describe those studies for which information was available. (No information on FY 72 funding was available for this report.) The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics:

- Clinical Evaluation of Lipid-Lowering Drugs. This study has involved the evaluation of the drug treatment of patients who have an elevated serum cholesterol or serum triglyceride. During the past year a resin called Colestipol was evaluated and found to be efficient in lowering serum cholesterol in a double blind study in which 50 percent of tne patients were given a placebo. Other drugs that may be useful in lowering serum triglyceride are to be studied.

- Studies on the Mode of Cholesterol Accumulation in Various Tissues of Rabbits with Moderate Hypercholesteremia. The study is designed to evaluate relationships among serum cholesterol levels and the degree of cholesterol accumulation in various organs. In relation to other organs and tissues, there was a rapid and avid uptake of cholesterol by the aorta--which may play a role in the pathogenesis of atherosclerosis.

- Studies on Cholesterol Metabolism in Rats by Application of D_2O and Mass Spectrometry. The experiment is designed to study the dynamic aspects of cholesterol metabolism in rats by application of D_2O and mass spectrometry. Thirty-six control rats were fed a cholesterol-free diet for three months and were then given a constant concentration (0 to 20 percent) of D_2O in their drinking water. Deuterium in atoms percent of body water, serum, tissue and fecal cholesterol was determined. Daily fecal output of neutral and acid sterols was also measured. The results showed no change in serum and tissue cholesterol concentration in control and experimental

groups in spite of the fact that the latter had a mean daily cholesterol absorption of 182 mg/kgm and a dietary contribution of 76 percent of the body exchangeable cholesterol.

- Studies on Serum Cholesterol Levels and Cholesterol Metabolism in Several Populations. These studies include extensive investigations of diet, serum cholesterol levels, cholesterol metabolism, and anatomical normal pathological examination in:

  - The Masai of East Africa...who exhibit low cholesterol levels (average of 227 levels= 135.4 ± 33.5 mg percent, with only seven over 200 mg percent) and a paucity of atherosclerosis

  - Alaskan Arctic Eskimos...whose mean serum cholesterol concentration (for 168 Eskimos) was 221 ± 66 mg percent.

  - Average U. S. Whites...This is a study of cholesterol metabolism only.

- Environmental Influences upon the Structure and Function of Human Blood Vessels. This VA and NHLI administered and funded study is focused upon the details of intramural lipoprotein degradation--using both physiological and electromicroscopic studies. (One concept regarding permeability and the development of atherosclerosis, suggest that lesions develop when the influx of lipids exceeds their clearance. The findings of this study are in accord with this concept.)

- Studies on the Role of Acid Mucopolysaccharides in the Pathogenesis of Atherosclerosis. A series of studies on the role of acid mucopolysaccharides (AMPS) in the pathogenesis of atherosclerosis and of the hormonal influences on the AMPS has been designed and partially carried out. These studies can be divided into several steps for testing various hypotheses.

- (Step 1) Studies on the changes of aortic AMPS during the course of atherogenesis induced by a high cholesterol diet in rabbits. Hypothesis--Elevated serum cholesterol will cause an overt influx of cholesterol into the aortic wall. β and pre-β complexes would form stable complexes with certain aortic AMPS and would be retained in the aortic wall. The retention of lipoprotein-AMPS complex initiates the atherosclerotic process which, in turn, produces more tissue damage and more production of AMPS.

- (Step 2) Studies on the effects of female sex hormones on the aortic AMPS and atherosclerosis in rabbits. Hypothesis--Two hypotheses for low incidence of atherosclerosis in premenopausal women are: (1) hypocholesteremic effect of estrogen, and (2) cyclic changes of estrogen and proesterone during the menstrual cycle inducing rapid turnover of aortic ground substance, which, in turn, prevents the development of atherosclerosis.

- (Step 3) Studies on the effects of thyroid hormone on the aortic AMPS and atherosclerosis in rabbits. Hypothesis--Thyroid hormone might increase the catabolism of cholesterol and turnover of aortic AMPS and hence might lower the serum cholesterol and decrease the severity of atherosclerosis.

- (Step 4) Studies on the effects of alloxan-induced diabetes mellitus on cholesterol metabolism, aortic AMPS, and atherosclerosis in rabbits.

- Studies on the Effect of Nicotine and Vitamin D on the Genesis of Dietary Induced Hypercholesteremia and Experimental Arteriosclerosis in Rhesus Monkeys. By applying multifactorial statistical methods, it was anticipated that the human variety of arteriosclerosis could be duplicated in rhesus monkeys by means of dietary hypercholesteremia, moderate hypervitaminosis D and chronic nicotinism. Due to the limitation of physical facilities, a modified factorial design was planned. Relatively safe dosages of vitamin D and nicotine were reached by the principle of trial and error. Preliminary results have shown:

- Hypercholesteremic responses to a diet containing 25 percent of coconut oil and two percent cholesterol were very impressive as compared to other studies. The addition of nicotine and/or vitamin D did not alter hypercholesteremic responses.

- Hypercholesteremia significantly increased the morbidity and mortality of monkeys receiving excessive vitamin D.

- Impressive arteriosclerosis with complications was observed only in animals receiving all three vascular toxins.

- Time of survival after exposure to the three vascular toxins has played a significant role in the severity of arteriosclerosis.

Animals surviving 26 weeks after the onset of hypercholesteremia and injection of vitamin D and nicotine administration developed arteritis and thrombosis of arteries of the legs. These studies are still in progress and should be completed within the next two years.

- Fundamental Research. The VA conducts in-house studies in this area.

Studies categorized as "fundamental research" include:

- Investigations of cholesterol synthesis. One of these studies has demonstrated that most of the partial reactions of cholesterol synthesis are carried out by cell-free preparations obtained from arteries of pigs and monkeys. These results demonstrate that arterial tissue is capable of synthesizing cholesterol. Whether this synthesis of cholesterol increases and is a major contributing factor in the development of atherosclerotic plaques remains to be determined.

- Investigations on the mechanism of control of the synthesis of fatty acids and cholesterol in mammalian liver. These studies have shown that changes in the rate of synthesis of enzymes effecting the synthesis of these compounds is the principal regulator of the rate of their synthesis. Furthermore, they have found that there is an inverse, but coordinated control, of the rate of synthesis of cholesterol and fatty acid synthesizing enzymes. Thus, when the rate of synthesis of cholesterol synthesizing enzymes is increased, the rate of synthesis of fatty acid synthesizing enzymes is decreased. Furthermore, the rate of synthesis of enzymes synthesizing cholesterol varies with the amount of fat in the diet. When diets are low in fat the rate of synthesis of cholesterol synthesizing enzymes is low in liver.

- Processes Which Can Influence the Acceleration of Cholesterol Modification in Atherosclerotic Tissue Relative to Normal Tissue. The VA conducts in-house studies in this area. These investigations include:

  - A study of the mechanism of cholesterol esterification by normal and atherosclerotic tissue. It was found that cholesterol esterification by normal and atherosclerotic tissue preparations, using palmitic acid as a substrate, required additional substances--adenosine triphosphate (ATP) and coenzyme A (CoA). At higher concentrations of palmitic acid another pathway for the information of cholesterol ester became evident; cholesterol esterification occurred without the need for ATP and CoA. While previous reports by another laboratory indicated that cholesterol esterification takes place by a third pathway (formation of cholesterol ester by the interaction of lecithin and cholesterol), this work does not confirm significant activity via this third pathway.

  - A study of the variance in susceptibility (from species to species) of different anatomical regions of the aorta to atherosclerosis. These VA conducted studies have indicated that the order of the magnitudes of the cholesterol-esterifying activities of aortic tissues derived from the rats, dogs,

rabbits and chickens did not correspond with the order of susceptibilities of these animals to atherosclerosis. Furthermore, the extent of the cholesterol-esterificating activities of the thoracic and abdominal aortas from the above species could not be correlated with the susceptibilities of these portions of the aortas to atherosclerosis.

- External Isotope Assay of Atherosclerotic Lesions. This project aims to develop a radioactive material for injection into the artery at the wrist which will detect, early in the teens and twenties, those patients most likely to suffer coronary attacks and strokes in later life. This has been accomplished in animals with an impure fat-detecting radio-dye; however, the pure synthetic radio-dye necessary for human use loses its radioactivity with purification. A remedy for this is being sought.

- Identification and Quantification of Dietary and Fecal Neutral Sterols by Mass Spectroscopy. The VA has devised a procedure for the identification and quantitation of dietary and fecal neutral steroids by the conformation of thin-layer chromatography, mass spectrometry, and Liebermann-Burchard colorimetry. The absolute quantity of each individual neutral steroid can be computed from the data obtained from the mass spectrum and colorimetry of the sample. The method is accurate and reproducible and of great value in the study of cholesterol metabolism even when the diet and feces contain a variety of plant steroids.

- Endogenous Fibrinolysis in Atherosclerosis. Preliminary studies have shown that there may be an imbalance between the clot-forming and clot-removal systems in patients with atherosclerosis. In some of these patients a relative depression in the clot-removal mechanism (endogenous fibrinolysis) has been found. This project comprises a large-scale study of patients in the VA and in the Cardiovascular Health Center Screening Program at the Albany Medical Center Hospital. The study now includes 850 individuals of all age groups. Of these, 690 show no evidence of atherosclerosis and 160 have definite clinical atherosclerosis. One or more blood samples

have been taken from each patient and analyzed by a variety of biochemical tests of the endogenous fibrinolytic system. Preliminary analysis of part of the data show that about two-thirds of the patients with atherosclerosis have deficient endogenous fibrinolytic activity while only about one-third of the normal group have deficient lytic activity. This is in agreement with previous findings. More complete analysis of the results is in progress with the assistance of the Albany Medical College Computer Center. Establishing the role of fibrinolysis in atherosclerosis, a disease which affects a large proportion of VA patients, will be of value in considering new modes of treatment of this disease.

- Development of Ultrasonic Drill--Bioinstrumentation. This project involves the development of an ultrasonic drill for cleaning the lumen of atherosclerotic vessels.

  Development of this drill continued during FY 72. The drill has been tested in vitro with specimens of human tissue. The apparatus has been developed to the point where it can deal effectively with the softer elements of atherosclerosis but not with calcified nodules.

- Study of Cholesterol Esterification in Atherosclerotic Tissue. Research at the VA Wadsworth Hospital Center, Los Angeles, California, is concerned with processes which can influence the acceleration of cholesterol esterification in atherosclerotic tissue relative to normal tissue. The extent of esterification in arterial tissue is dependent in part on the concentration of fatty acyl-CoA. Oxidation of fatty acyl-CoA by an atherosclerotic tissue preparation was impaired as compared to the normal, suggesting a larger concentration of fatty acyl-CoA in atherosclerotic tissue.

1.2 CORONARY HEART DISEASE

1.2.A Coronary Heart Disease--Department of Agriculture

No identified ongoing USDA research is directly related to this area.

1.2.B Coronary Heart Disease--Atomic Energy Commission

In FY 72, AEC funded and administered four types of programs related primarily to coronary heart disease:

- Epidemiological Study of Coronary Heart Disease, Cerebrovascular Disease and Hypertension in Hiroshima, Nagasaki, Hawaii and San Francisco. The Atomic Bomb Casualty Commission (ABCC) in Japan is collaborating in a cooperative epidemiologic study of coronary heart disease, cerebrovascular disease, and hypertension in Hiroshima, Nagasaki, Hawaii, and the San Francisco Bay area. The major objectives are to assess the reported cardiovascular disease mortality due to these diseases in population groups and to investigate in detail the presumed risk factors as they are manifested in the populations under study. At present, the study is in the stage of data collection relative to the prevalence of cardiovascular disease, incidence of myocardial infarction, biochemical findings, and characterization of diet. The study is jointly funded by NHLI and AEC. Other research conducted by the ABCC in related areas is supported solely by the AEC.

  In FY 72, the AEC funded and administered one onsite contract totalling $90,000. During this period non-AEC support of this ABCC study (support from NHLI) was $45,000.

- Artificial Heart Studies. An artificial heart powered by plutonium-238 is currently being developed by the AEC's Division of Applied Technology.

  In FY 72, the AEC funded and administered eight contracts, totalling $1,541,000 (three onsite contracts, $515,000; five offsite contracts, $1,026,000), dealing with the development of the nuclear fuel, heat source technology, a study of thermal converter practicability, and a study of recipient and population radiation exposure.

- Biological Research: Adverse Effects of Radiation and Heat from the Power Source of an Artificial Heart. Accompanying the development of the nuclear-powered artificial heart is biological research (in dogs and minature swine) on possible adverse effects produced by radiation and heat released by the power source.

  In FY 72, the AEC funded and administered two contracts, totalling $152,000 (one onsite contract at the Pacific Northwest Laboratory, $50,000; one offsite contract at Cornell University, $102,000), dealing with this subject. Research at the Pacific Northwest Laboratory on heat effects from implanted nuclear power sources was also supported by NHLI (FY 72: one contract $50,000).

- Nuclear Medicine Technology. The Atomic Energy Commission funds and administers contract-supported research in nuclear medicine technology (FY 72: four onsite contracts, $2,566,000; three offsite contracts, $94,000).

  Ongoing research in nuclear medicine technology includes work on the development of radioisotopic techniques for the early detection of abnormalities in the cardiovascular system. A variety of radiopharmaceuticals and techniques are being tested in an effort to detect early changes in cardiac function and to assess myocardial integrity. Among the promising developments is radioisotope angiocardiography, which is under study in several laboratories.

In one laboratory, nuclear medicine techniques are being used to study the kinetics of new blood vessel formation in myocardial tissue during various stages of myocardial infarction. Several groups are working to develop radioisotopic techniques for the quantification of regional blood flow in the brain and other organ systems. Supporting these clinically oriented studies is general research on nuclear medicine technology that applies to various specific diseases. The program described here relates to a number of different problem areas discussed in the Heart and Blood Vessel Diseases Panel report, particularly in the areas of atherosclerosis, coronary vascular disease, hypertension, stroke and cardiac failure.

1.2.C Coronary Heart Disease--Department of Defense

In FY 72, the Department of the Army conducted two projects (funded at $560,000) with a significant relationship to coronary heart disease:

- One project is devoted to:
  - Cardiovascular dynamics i.e., studies of hemodynamic and biochemical controls of the normal heart and its coronary circulation under a variety of normal and abnormal stresses encountered
  - Epidemiological studies of the natural history of the development of coronary arterial collateral circulation in the presence of induced coronary insufficiency and studies of ways to improve such collateral compensation.
- Clinical Evaluation of Responses of the Body to Combat Injury. This project includes studies of the constructed distal arterial-venous fistula in venous reconstruction in dogs showing a significant drop in distal arterial pressure and flow. Heparin and low molecular weight dextran were shown to marginally improve the patency rates of canine autogenous vein grafts; and prolonged femoral venous occlusion resulted in persistent low femoral arterial flow until the release of the occlusion in the dog.

NHLI

In FY 72, the Department of the Air Force funded and administered three studies related to coronary heart disease:

- Cardiovascular Disease in Officer Personnel, the objective of which was to determine whether absolute levels of various blood lipids and/or patterns of changes in lipid parameters had predictive value in the development of cardiovascular disease. This is a longitudinal study which has been conducted since 1952 on a cohort of 479 graduates of the United States Military Academy. (FY 72 funding: $38,000)

- The Noninvasive Assessment of Coronary Artery Disease. (FY 72 funding: $13,000) Techniques have been developed for imaging the myocardium following intravenous injections of potassium 43. In normal patients a uniform homogeneous pattern of potassium 43 uptake indicating normal myocardial perfusion has been documented. This pattern is unchanged following exercise. In patients studied with transmural myocardial infarction, regions of decreased potassium 43 uptake corresponding to electrocardiographic and angiographic sites of infarction have been demonstrated.

- Angiographic and hemodynamic findings in the young patient with coronary artery disease (funded by local operating resources).

1.2.D Coronary Heart Disease--Environmental Protection Agency

The EPA funds and administers a Pesticide Epidemiology Program which is composed of 13 contract supported studies (Fy 73: $3,101,101). Four major types of activities are being undertaken:

- Community Profiles--pesticide usage patterns, morbidity and mortality patterns in the geographic areas are being studied.

NHLI

- Residue analysis of general populations and acute poisoning investigations (including interstitial fibrosis caused by perquad and diquad).

- Prospective and biochemical health surveillance of people occupationally in contact with pesticides (3,000 subjects being followed) from manufacturing of pesticides through farm usage. Medical exams including 6 enzyme analyses and 16 biochemistries are performed annually for the participants.

- Special studies: e.g., study of coronary arterial effects of pesticides, percutaneous penetration studies, animal model (squirrel monkeys) for low dosage effects, and pathological analysis of residues in fats (organo-chlorines, organo-phosphates).

A study was initiated in FY 73 to correlate water quality data (hardness versus softness) with previously obtained data on cardiovascular disease mortality. A literature review has been completed. Twenty thousand dollars has been allocated for FY 73.

A cooperative study is being undertaken with the Epidemiology Branch, NHLI to analyze water quality data such as lithium, calcium, sodium, etc., to determine the relationship between drinking water quality and mortality from coronary heart disease.

The Community Health and Environmental Surveillance Studies (CHESS) of the Human Studies Laboratory of EPA (See Section 2.2.D for description of CHESS) includes analyses of the effects of atmospheric pollution on persons with chronic heart diseases.

The Human Studies Laboratory of EPA conducts Clinical Laboratory Programs (See Section 2.1.D for description) which include:

- Effects of carbon monoxide on coronary artery disease
- Effects of carbon monoxide exposure on the outcome of myocardial infarction (in humans and in monkeys).

1.2.E Coronary Heart Disease--Food and Drug Administration

No identified ongoing FDA supported research activities are related to this area.

The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

1.2.F Coronary Heart Disease--Health Services and Mental Health Administration

The Regional Medical Programs Service, HSMHA funded and administered programs for coronary care demonstrations and training in 37 regions with 77 projects in FY 72. Total funding in FY 72 was approximately $4,275,000 in this category.

Other areas of HSMHA involvement in coronary disease have included:

- Cardiopulmonary Resuscitation Training (eight projects in FY 72, totalling $266,613).
- Electrical Safety in Cardiac Care Units (four projects with FY 72 funding at $46,000).
- Pacemaker Clinics (two projects in FY 72, totalling $106,774).

- Long distance transmission of ECGs and catheterization data (four projects in FY 72: totalling $460,000)

- Upgrading of ambulance capability and emergency personnel training, including the handling of coronary emergencies (28 projects in FY 72; totalling $8,360,000).

The National Institute of Mental Health (NIMH), HSMHA, funds and administers research related to coronary heart disease.

Among these NIMH supported research projects are:

- A Study of Psychiatric Aspects of Coronary Artery Revascularization (FY 72: one grant totalling $22,000). This study examines personality structure and response to emotional stresses between catherization and cardiac surgery which influence clinical results. The stress studies include psychiatric data, patient self-ratings, psychoendocrine response analyses, postcatherization venous sampling, results of the Hackett-Cassim Denial Scale, Cattell 16 PF Questionnaire, Jenkins activity survey for health prediction, and postcardiotomy delerium evaluation. Decliners are used as a control group.

- Experimental Studies of Long-Term Stress (FY 72: one grant totalling $55,615 [approx.]). This investigation is designed to study the effects of long-term stress on behavior and on physiological functioning. Specific focus is on how different types of stress affect both conditioned and unconditioned responses, and how stress may cause the development of hypertension, coronary disease, and ulcers. Human subjects, rats, and monkeys are studied. Studies include investigation of the effects of increasing shock intensity upon test animals' accuracy of discrimination, and the effects of presenting shock and not warning that it is forthcoming. Humans are asked to withstand as much shock as possible after being told that their pay will increase proportionally to the level of shock they can tolerate.

- Instrumental Learning of Cardiovascular Responses (FY 72: one grant, totalling $74,723). This investigation continues an earlier study of the instrumental learning of cardiovascular responses. The primary aim of the project is to develop experimental models of heart disease in animals in order to identify the neural and hormonal mechanisms controlling heart rate and blood pressure. The investigation also examines the feasibility of using such visceral learning in the therapy of experimentally induced hypertension. It also attempts to determine if the learning of visceral responses in infant animals influences the development of characteristic adult stress reactions. Rats, rabbits, and cats are used in the experiments (for additional related effort see Section 1.9.F).

1.2.G Coronary Heart Disease--National Aeronautics and Space Administration

The NASA interest is not in coronary heart disease per se but rather in the evaluation and understanding of the normal cardiovascular function and deviations from this normal baseline. Descriptions of their studies should be read from this point of view. Nevertheless their work is applicable to this area and may be considered in two general categories (1) instrumentation and (2) biological functions.

In FY 72, the NASA funded and administered six programs (FY 72 funding: $475,000) directed at the development of diagnostic instrumentation and equipment for cardiovascular measurements. The studies were:

- Advanced Cardiovascular Bioinstrumentation in Man. Advanced cardiovascular instrumentation has been developed for measurement of human central and peripheral cardiovascular function by noninvasive techniques. These methods include measurement of cardiac

output and left ventricular dimensions by echo-ultrasound, venous pressure by transcutaneous Doppler ultrasound and peripheral velocity flow profiles and vessels dimensions by pulsed Doppler ultrasound. These methods are presently under evaluation in the laboratory and on the bench for accuracy and reliability of measurements. Other methods such as multiple level ECG for use in body surface mapping studies as a determination of heart volume and hematocrit are under early investigation. The technical objectives of the project are to:

- Develop flight qualified hardware to measure cardiac and peripheral vascular functions by non-invasive techniques

- Qualify developed instruments for accuracy and reliability.

The approach is to test models under laboratory and bedside conditions, to develop advanced fabrication and instrumentation methods, and to test hardware against accepted standards for calibration for use under clinical conditions.

- A Feasibility Study of a Microwave Regional Blood Volume Sensing Technique. Noninvasive means for obtaining regional blood volume and blood flow in humans is difficult to obtain and hampered by lack of adequate and reliable instrumentation techniques. It is the purpose of this study to develop microwave radiometers for these applications. These methods are applicable for use during spaceflight but particularly for use while subject is enclosed within a space suit. The technical objectives of the study are:

  - To develop microwave radiometers for sensing regional temperature changes from the body surface from which blood volume and blood flow in humans may be derived.

  - To adapt these systems for use in orbital flight.

The approach is that sensitive microwave radiometers will be developed for laboratory use and applied to phantom models of human tissue, optimum operating frequency over the range 0.5 to 5 GH_Z will be determined, sensitivity of 0.5°K rms. will be chosen for 20-second integration interval, and instruments will be tested in animal and human subjects.

- Noninvasive Measurement of Central Venous Pressure. It is the objective of work in this area to continue development of noninvasive ultrasonic instrumentation to study venous properties in the arm. It is hypothesized that changes in venous properties occur as a consequence of weightlessness and spaceflight. It is the purpose of this task to develop such technology and apply it to human subjects at rest and subsequent to bedrest simulation of weightlessness. The technical objectives of this project are:

  - To develop ultrasonic methods for measuring central venous pressure in man

  - To apply these methods under spaceflight conditions.

  The approach is:

  - Transcutaneous Doppler ultrasonic flow transducers and electronics will be modified and arranged in optimal configuration for determining venous flow velocity in the arm

  - Flack tester will be developed for providing gradual and increased intrathoracic pressure in forced expirations

  - Point of cessation of venous flow velocity and measured intrathoracic pressure will be compared with simultaneously recorded venous pressure in the arm.

- Ultrasonic Doppler Measurement of Renal Artery Blood Flow. Study of blood flow and its distribution to specific organs in awake unrestrained animals has been hampered by a lack of appropriate instrumentation for these purposes. Recent technologic advances demonstrate that this may now be accomplished by the use of chronically implanted flow transducers and a radio telemetry link. Work will be focused on the use of Doppler flow systems for these purposes which allow for the determination of flow velocity profiles in instrumented vessels as well as their cross-sectional area. Units will be developed capable of chronic implantation in animals and eventually in man for these purposes. Determination of renal blood flow in man is considered an important and primary factor in the understanding and determination of the mechanisms operative in producing the diuresis observed subsequent to weightlessness and bedrest. The kidneys represent an organ system placed reasonably close to the body surface so they are more readily accessible to study by transcutaneous techniques.

- Study for Vectorcardiogram Display System and Blood Pressure Monitoring Systems. The objective of this effort is to design and develop a new system of a vectorcardiogram (VCG), and a beat-by-beat blood pressure measurement instrument. The VCG system will allow further interpretation of data heretofore not possible and the blood pressure measurement system will permit the continuous monitoring of blood pressure thereby allowing greater resolution of control mechanisms. These systems will be applicable to both space and clinical medicine. The contractor is developing a system capable of acquiring and displaying vectorcardiograms in a flexible form including three dimensional perspective. In addition, the system will include an ability for quantitative examination of the vectorcardiogram. Stereoscopic displays of individual VCG complexes on the standard anatomical axes will be made possible on an oscilloscope; numerical values for the areas of the projected loops and the mean axis of the loops will be computed. To evaluate the system's capability, a test plan will be developed using both normal and abnormal subject data. Following verification,

a functional VCG system will be assembled and furnished to the Cardiovascular Laboratory. The contractor will also design and develop a portable and noninvasive beat-by-beat blood pressure measurement system.

- Feasibility Study of Limb Volume Measuring Systems. This research seeks to develop new, more accurate, and readily applicable to inflight use, methods for plethysmography, particularly of human limbs. (Plethysmography is important to evaluation and understanding of cardiovascular changes consequent to spaceflight.) Current methods lack either precision, general applicability, or specific capability for inflight use. Investigators will reevaluate existing methods of plethysmography, examine and originate additional concepts, determine most feasible and promising new avenues, design and build operational prototypes, and recommend to NASA a best technique.

The Biomedical Research Division, NASA, funds and administers contract supported studies related to biological functions as follows:

- Neurohumoral Control of Cardiovascular Responses (FY 72: one contract, totalling $90,000).

  The study is designed to:

  - Produce awake, unanesthetized, unrestrained dogs and chimpanzees instrumented in such a way that primary cardiovascular parameters (re: hydraulic performance of the heart and peripheral circulation) can be measured for periods in excess of one year

  - Develop a method for provocative stimulation of cardiovascular responses in unrestrained animals.

  The approach involves several procedures including:

  - The preparation of chronically instrumented dogs to provide information concerning ventricular

and/or atrial pressures, cardiac dimensions, ventricular flow and wall thickness

- The measurement of responses to rest, exercise, administration of selected drugs and aortic root construction.

- Regulation of Blood Flow Distribution: (FY 72: one contract, totalling $20,000). The objective of this study is to define mechanisms by which distribution of total and regional blood flow is regulated in relation to metabolic (O_2 transport) and physical needs (heat loss) and various combinations of the two. This study is designed to determine the importance of reflex control of blood pressure via baroreceptors in explaining the altered distribution of blood flow in hyperthermia. The splanchnic and skeletal muscle bed, particularly, are being considered.

- Biocybernetic Model of the Cardiovascular System During Headward and Footward Acceleration (FY 72: one contract, totalling $40,000). The study objective is to develop a computer-based model of the response of the cardiovascular system to acceleration and tilting. Prior to the undertaking of this study no model existed to relate the effects of gravity and/or acceleration to the cardiovascular changes observed on reentry from spaceflight (Apollo or proposed shuttle) or postflight tilt tests. It is the purpose of this study to develop a computer-based model of the response of the cardiovascular system to acceleration. Such a model will be used to integrate knowledge now scattered throughout the literature and allow for prediction of acceleration limits and tolerances in new and novel situations. Both animal and human models are to be constructed.

- Studies of Left Ventricular Function and Vasodepressor Syncope (FY 72: one contract, totalling $100,000). The objective of this study is to develop methods and techniques to evaluate left ventricular function and vasodepressor syncope. To date:

  - Peripheral venous scintillation angiocardiography is being utilized to determine left ventricular cardiac volume in man and correlate findings with present standard methods of ventricular volume determination

- Apex cardiography in man has been studied in normal controls, in cardiac patients and in normal bedrest subjects representing a noninvasive technique to achieve an index of ventricular contractility

- Studies of vasomotor wave activity as related to vasodepressor syncope have been carried out with a high gain impedance plethysmograph.

NOTE: Scintillation angiocardiography has shown promise as a method for evaluating ventricular function and will be further evaluated. Apex cardiograph has been demonstrated to be a good index of cardiac contractility and study will continue on bedrest subjects. The vasodepressor syncope study will continue but with an ultrasound technique rather than the plethysmographic technique since the latter method proved to be unsuitable.

- Investigation of Atraumatic Techniques for Monitoring Cardiovascular Status and Conditioning (FY 72: one contract, totalling $25,000). The objective of this study is the development of nontraumatic monitoring methods and validation for their use in the space environment. Cardiovascular system elements critical to space adaption have no such currently available measurement techniques. Practically useful methods and techniques are needed for use in pre- and post-flight space crew evaluations, while refinements and extensions should be programmed for future long duration missions.

  Redefinition of old elements used to describe cardiac status and defining new descriptors which will allow more accurate and immediate determinations for application to space activities are needed. These will be based upon ease and reproducibility of application of sensors, basic merit of physiologic measurement, feasibility of flight hardware development, and amenability of data reduction for real time monitoring.

  Progress: This contract was initiated October 1969. The contractor has extended his work to large series of subjects after successful results from pilot studies utilizing multiple noninvasive measurements of cardiovascular responses to various stresses. Several scientific publications have resulted.

- Cardiovascular Hemodynamics in Man (FY 72: one contract, totalling $90,000). This study is comprised of investigations which are being conducted in man to determine accuracy of various methods for indirectly determining hydraulic cardiac performance by noninvasive methods. Such methods (ultrasonic) are being proposed for use during manned space flight to measure ventricular and/or atrial dimensions, cardiac output and central venous pressure. These methods are being evaluated against standard laboratory techniques to determine accuracy and repeatability of measurement. Studies using these techniques are being conducted in bedrest simulations of weightlessness.

  The technical objectives of this study include:

  - The development of noninvasive methods for determining cardiac functions in man
  - The conduct of human studies to determine accuracy of various methods for indirectly determining hydraulic cardiac performance
  - The testing of methods in bedrest studies to accumulate ground-based information using various methods
  - The qualification of methods for inflight use.

  Subjects with heart disease of varied etiologies are being studied during cardiac catheterizations in order to compare standard methods for determining cardiac output (Fick method) and dynamic geometry (angiocardiography) against ultrasonic measurements. Ultrasonic methods for detaining venous pressure are also being measured.

1.2.H Coronary Heart Disease--National Science Foundation

In FY 72 the NSF funded and administered three programs (FY 72 funding: $44,600)* directed at a basic understanding of cardiac function. In addition, projects under Atherosclerosis (1.1.H) are applicable.

* Reflects two programs only: neural mechanisms of cardiac conditioning, and myofibrillar assembly in cardiac muscle.

- Neural Mechanisms of Cardiac Conditioning. The long-term goal of this research program is to investigate conditioned cardioacceleration as a model for cellular neurophysiological studies of learning. To continue analysis of the properties of the heart rate response, the heart rate orienting response in the pigeon and its relationship to the conditioned heart rate response will be studied. Recent lesion data suggest that these responses may in part be mediated by different neural pathways. Two other planned studies relate to the analysis of interactions of the heart rate response with accompanying conditioned responses. In one, conditioning performance will be assessed with surgical cardiac denervation to determine whether conditioned release of catecholamine affects the heart rate response. This is a follow-up of a previous denervation study that excluded all non-neural contributions except those that may be mediated through the beta-receptors. The other study entails investigation of the relationship of the heart rate response to conditioned changes in blood pressure. Also, a series of experiments to continue mapping the neural pathways mediating the conditioned cardioacceleratory response will be carried out. These involve:

  - Further definition of the relevant visual pathways transmitting the conditioned stimulus information

  - Continued study of the efferent pathways

    Preliminary investigation of the somatosensory pathways transmitting the unconditioned stimulus information.

- Myofibrillar Assembly in Cardiac Muscle. There is an increasing body of knowledge linking up the biosynthesis of the major myofibrillar proteins with their striking properties of self-assembly in vitro. There is now fairly good evidence that the myofibrillar proteins, once synthesized, polymerize intracellularly to form the characteristic thick and thin myofilaments of the myofibril. These filaments are then organized into the precise, double hexagonal array of the striated muscle sarcomere.

The specific aims of this research are

- To analyze the mechanism of the intracellular disassembly of myofibrils during trypsin-induced dissociation of embryonic heart tissue

- To develop a method for the complete disassembly of myofibrils in 100 percent of the dissociated heart cells--without significant intracellular proteolysis of myofibrillar proteins

- To quantitatively assay the intracellular reassembly of myofibrils

- To establish an in vitro system for obtaining myofibrillar assembly (applicable also to cardiac failure and arrhythmia).

- Cardiopulmonary Dynamics*. Basic mechanical properties of the heart and lung tissues are being determined. This includes the stress-strain relation, stress relaxation under constant strain, creep under constant stress, hysteresis in cyclic loading, the velocity-tension-length-time relationship of the contractile element of the cardiac muscle, the same for the vascular smooth muscle, the elasticity of the parallel and series elements of these muscles, and the "active state" function of these muscles. The dynamics of pulmonary surfactant will be determined also.

  A rational theory will be formulated for the dynamics of the heart and the lung taking into account the structural arrangement of the cardiac muscle fibers, the alveolar structure of the lung, and the mechanical properties as determined above. A full theory will be developed against which various simplifying assumptions may be checked. Theoretical deductions will be explored and compared with in vivo experiments. The comparison will undoubtedly suggest courses for further development and improvement.

  After the basic theory is satisfactorily verified, it will be developed into a concise form which could be used by physicians and surgeons in clinical conditions (also applicable to Section 1.3.H, Peripheral Vascular Disease, and to Section 1.10.H, Cardiac Failure).

* Dollar totals for this project counted under 2.1.H

1.2.I Coronary Heart Disease--Social and Rehabilitation Service

The SRS funds and administers three types of activities related to coronary heart disease: (1) Categorical Research and Demonstration Projects; (2) Rehabilitation Research and Training Center Activities; and (3) International Studies supported by P.L.480. Some of this work is also applicable to other areas, especially rheumatic and other valvular heart diseases.

Categorical Rehabilitation Research and Demonstration Projects related to coronary heart disease are:

- Exercise ECG Parameters in Cardiac Rehabilitation. The purpose of this project is to evaluate the exercise ECG as a clinical tool to determine safe activity levels and assist in the rehabilitation of cardiac patients ($100,000)

- Work Tolerance Evaluation Research Unit. To demonstrate how to establish and develop a work tolerance unit in a multidisciplinary rehabilitation setting ($100,000)

- Critical Selection of Heart Surgery Patients for Vocational Rehabilitation. To determine which predictive factors are most effective in selecting heart surgery patients for vocational rehabilitation ($75,000)

- Rehabilitation of the Patient with Severely Disabling Angina. To determine the benefits of bypass surgical intervention upon the rehabilitation of persons with ischemic heart disease ($100,000)

- Rehabilitation of Patients with Ischemic Heart Disease. To determine the benefits of various modalities of treatment for rehabilitation ($150,000)

- Adaptation of Coronary Subjects to Intervention Programs. To evaluate the effects of graded, standardized exercise upon the rehabilitation potential of post MI patients (no funding data available).

The Rehabilitation Research and Training Center Activity (funded at $1,050,000 including some research and demonstration funds) related to coronary heart disease is entitled "The Effects of Physical Activity on the Rehabilitation of Post-myocardial Infarction Patients." The objective of the study is to determine the effects of physical conditioning of postmyocardial patients (3,000 or more: 1,500 in the control group and 1,500 in the treatment group) on the development of complications and/or recurrences of myocardial infarctions or other coronary events and the overall mortality from all causes for a period of five to seven years.

The International Rehabilitation Studies (P.L.480) related to coronary heart disease are:

- The effects of exercise tests on sedentary employees, laborers and farmers in Egypt ($75,000)

- A study of the influence of physical exercise in reducing the incidence of coronary artery disease in Israel ($100,000)

- A study of the influence of a rehabilitation program on patients with myocardial infarct in Yugoslavia ($75,000)

- A rehabilitation center of young cardiac patients in Morrocco ($75,000)
- A study of rehabilitation of patients with coronary insufficiency in Yugoslavia ($75,000)
- A study of physical exercise in rehabilitating post-coronary patients in Israel ($40,000)
- A study to establish a work evaluation unit for patients with heart disease and to determine energy requirements of commonly indigenous jobs in Pakistan ($103,207)
- A comparison of methods for rehabilitation of patients with myocardial infarction in Poland ($100,000)
- A study of means of affecting certain risk factors in coronary patients and in otherwise healthy but coronary prone individuals in Yugoslavia ($113,793).

The SRS provides third party payments for provision of care (which may involve participation in clinical research).

1.2.J Coronary Heart Disease--Social Security Administration

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

1.2.K Coronary Heart Disease--Department of Transportation

The Federal Aeronautics Administration funds and administers four programs (FY 72: two contracts, totalling $605,000; two in-house projects, totalling $119,000) related to coronary heart disease:

- Stress and Fatigue in Aviation Activities. To correlate ECG, blood pressure, and oxygen consumption with aircraft simulation flight

- Early Detection of Incipient Coronary Heart Disease in Aviation Personnel. To determine means of discovering covert coronary disease by certain ECG and computer techniques

- Health Study of Air Traffic Controllers. To determine onset and correlation of stress aspects of air traffic control including cardiovascular and hypertensive changes

- Development of a System to Scan, Digitize, and Store ECG Records. To determine a means of converting clinical ECG's received by mail to digital format for screening.

1.2.L Coronary Heart Disease--Veterans Administration

The VA funds, conducts and administers numerous studies related to coronary heart disease. (No information on FY 72 funding was available for this report.) The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics.

The studies include:

- Cooperative Study--Short Term Use of Anticoagulants Following Myocardial Infarction. This study has now been completed. A total of 1,026 patients were randomized. All records have been reviewed by the Review Committee, and have been sent to the Statistical Department of the University of Minnesota for coding. The final manuscript and data tables are being prepared for submission to the Journal of the American Medical Association.

  Preliminary results of this completed cooperative study on anticoagulants during the acute phase of myocardial infarction show the following:

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- Death rate is not altered

- There is a significant reduction in blood clots to the lung and brain in treated patients

- The number of repeat heart attacks (coronary thromboses) is not reduced

- There were no major bleeding episodes.

These findings have great significance in the therapy of this disease since it permits the physician to treat only those patients particularly susceptible to thromboembolic complications (blood clots) with anticoagulants. Final analyses of the results should provide the physician with certain guidelines to identify those patients who will benefit from such therapy.

- Study of Myocardial Infarction and Coronary Blood Flow. The purpose of this study is to determine if, after an acute myocardial infarction, prompt return of blood flow will prevent extensive damage to the heart muscles, and thereby improve the chances of surviving after a heart attack and improve the chances of leading a more normal life following the attack. The answer to this important question has become relevant in the last two or three years as methods have now developed which can restore blood supply to areas of the heart suffering from diminished blood flow.

- Cooperative Study of Surgical Treatment of Coronary Artery Disease. This study was intensified during the past year in the continuing effort to determine the effectiveness of the current surgical procedures used for coronary arterial atherosclerosis. Emphasis was mostly on the aortocoronary saphenous vein bypass graft. A thorough evaluation of the progress of this study was made during the course of this year by an independent body, and it was recommended that the study be continued for two more years.

  Some 4,000 veteran patients had been screened by the end of FY 72 and over 1,000 of these had received coronary arteriography. Nearly 600 patients had been entered into the study at this writing.

Careful monitoring of both coronary arteriography and of the surgical procedures involved was carried out during this past year. As a result of this continuous scrutiny, a substudy of the complications of coronary arteriography evolved, which led to the recognition of some of the hazards of coronary arteriography, and its relationship to the techniques used. This portion of the substudy was brought to the attention of the medical profession at the end of FY 72. A second substudy to determine the degrees of uniformity of interpretation of coronary arteriograms is also undergoing analysis.

This cooperative effort by 15 VA hospitals is the first large-scale planned attempt to determine in an objective manner whether or not the operative procedure which is being done in great numbers in many centers in the country has an identifiable effect on either the morbidity or mortality from coronary arterial disease, one of the most common of cardiac diseases seen in VA patients. The pattern of this protocol is being studied in the planning of other similar studies, still in the nonoperational stages. It is hoped that data will be available from this study which can be relied on by practitioners in helping them make decisions as to the proper management of this difficult disease.

NOTE: Some patients receive surgical therapy but all receive careful periodic examination, lipid determination, periodic EKG and chest radiograph. Attention is given to correction of diet. Exercise programs are prescribed as well as select medication.

- Computer Study of the Surgical Treatment of Valvular and Coronary Heart Disease. At present, approximately 500 patients have been reviewed and the data has been partially analyzed (patients with coronary artery disease who have undergone vein bypass operations at UCLA and at Wadsworth VA Hospital are included in this study). The primary purpose is to improve case selection by analyzing preoperative data in relation to postoperative results. In patients undergoing cardiac valve operations, it has been found that long duration or preoperative symptoms has been associated with poor postoperative results. Accordingly, earlier

operation is being offered to some patients in order to avoid the development of irreversible disability. In patients with coronary artery disease, those who have had disease in all three major coronary arteries and previous myocardial infarctions have had poor results. The goal in these studies is to identify patients with high risk factors before they develop severe myocardial infarctions, which may also cause permanent disability.

- Resting and Exercise Left Ventricular Function in Coronary Artery Disease. The purpose of this study is to quantitate left ventricular function at rest and during exercise in patients with coronary artery disease. These studies are being done in all patients studied in a VA catheterization laboratory and are being repeated in those patients having bypass surgery one year after surgery. The protocol consists of measuring resting hemodynamics, hemodynamics during subpain exercise, quantitative left ventricular biplane angiocardiography, and coronary arteriography in this sequence. During the past year, approximately 100 patients with clinical and angiographic coronary artery disease have been studied in the above manner. Various parameters of left ventricular function are now being correlated with coronary angiographic morphology, surgical mortality, and clinical status. They will also be used to evaluate the effects of coronary bypass surgery.

  Preliminary evaluation of the data shows that 76 percent of the patients have an abnormal ejection fraction, 79 percent an abnormally large end-systolic volume, 80 percent an abnormal exercise A-V oxygen difference, and 54 percent an abnormal exercise wedge pressure. All of the patients have at least one of the above abnormalities. Thus, the sensitivity of this evaluation is very high. Attempts are being made to quantitate the coronary arteriograms. These data will then be correlated with the above left ventricular function measurements.

- Dial-A-Diagnosis Program. This is a research program primarily aimed at developing software packages for the computer-assisted aid in diagnosis. This is a joint effort with the Health Care Technology Division, Department of Health, Education and Welfare, Public Health Service, Health Services and Mental Health Administration. To date, it is possible to develop logic for a solution of particular medical problems with the computer aiding and leading the physician through a particular diagnostic situation. For example, while it may be difficult for some doctors to keep in mind the coagulation mechanisms, it is possible to sit down and develop software packages that can lead a physician through the entire sequence so that at the end a specific factor deficiency can be determined.

  Definite types of computer logic have been used in the development of these software packages:

  - Branching logic
  - Decision matrices
  - Specific weights determined from discriminant function analysis.

  It has been noted that various types of medical problems require different types of logic in order to achieve the results. To date, there are about 30-40 software packages that have been developed, which include:

  - Mortality in Acute Myocardial Infarct
  - Hyperthyroid Diagnostic Index
  - Framingham Coronary Heart Prognosticator
  - Intravascular Coagulation Defects
  - Three-Year Prognosis for Acute Myocardial Infarct
  - Prediction of Aortic-Ventricular Gradient
  - Hypertension

- Calculation of Plasma Osmolality
- Mean and S.D. Program
- Treatment Plan for Acute Respiratory Acidosis
- Respiratory Acidosis
- Characterization of Avid Base Problems
- Three-Year Coronary Prognostic Index (C.P.I.)
- Chest Pain--Doctor's Version
- Chest Pain--Patient's Version
- Classification of Arrhythmia
- Classification of Hyperlipidemias
- Correlation Matrix
- Correlation Coefficient

- Development of a Pressure Flow Catheter. Studies have resulted in a cardiac catheter being developed and utilized in patients which allows simultaneous recording of instantaneous pressure, flow, and the phonocardiogram. On-line computation of cardiac and vascular parameters indicate the tone of the vascular tree and the power of the heart. This device provides previously unavailable data leading to increased quality of patient care in the areas of cardiovascular disease and trauma.

- Noninvasive Monitoring of Cardiac Function. It is of utmost importance to develop bedside methods which could measure the force and the output of the heart as easily as an electrocardiogram. One of such methods developed uses the short-time intervals during the contraction of the heart muscle by measuring heart sounds and the pulse wave over the carotid artery. In the past results with this method were not reproducible and therefore new landmarks have been introduced to measure the force and output of the heart. These consist of electrical impedance measurements over the

chest and of heart sounds of extremely low frequencies. This new bloodless technique will be applied in normal volunteers and in patients with coronary heart disease. The information will be immediately available to the physician by the digital readout of an on-line-computer or a small solid-state system.

- Computer Analysis of Noninvasive Technique. Considerable progress has been made in VA-conducted research in developing on-line systems for handling noninvasive techniques. Software programs have been developed on line which immediately printout such things as systolic time interval, along with predicted values, for immediate use in research as well as to aid in patient management and diagnosis. Printouts of average systolic and diastolic slopes measured from carotid pulse pressures are accompanied by a statement giving the probabilities that these slopes belong to various disease groups (normal, aortic stenosis, aortic insufficiency, hypertrophic aortic stenosis, combined aortic stenosis--aortic insufficiency).

  A program using the kinetocardiogram for the diagnosis and quantitation of various cardiovascular diseases is in development.

  A software package has been developed which basically compares curves from the various diagnostic conditions. It appears to have an accuracy of somewhere around 70 percent at the present time. As mentioned above, the software package for the termination of systolic time intervals from the electrocardiogram, carotid pulse and heart sounds has been completed and is in daily operation, with immediate printouts back to the physician. A software package has been developed for the ballistocardiogram which recognizes the various wave forms, calibrates the curve in cm/sec^2, and measures various time intervals between the waves. The output of this program serves as data for studies concerning the ballistocardiogram. Several of these have been completed, such as the use of the ballistocardiogram, quantitation and aortic stenosis.

- Studies on Aortic Compliance. Among the studies in this area conducted by the VA are:

- Studies on the Response to Single Segment Intra-aortic Balloon Pumping as Related to Aortic Compliance

- Studies on Aortic Compliance and Its Relationship to Aortic Constituents in Man.

- Evaluation of Group Psychotherapy in Post Heart Attack Patients. Group psychotherapy for patients who have recently experienced a heart attack has been evaluated. In this study 25 patients were selected. Eleven patients met weekly with a psychologist and received standard medical therapy. All of these patients are living and well. The control group of 14 patients just received standard medical therapy. Three of the patients in this group died during the first year of the study. Blood pressure tended to fall in the treatment group, but tended to rise in the control group. This study will be combined with 120 patients from another source. All patients will be followed for a four-year period before final conclusions are made.

1.3 PERIPHERAL VASCULAR DISEASE

1.3.A Peripheral Vascular Disease--Department of Agriculture

No identified ongoing research efforts of the USDA are directly concerned with this area.

1.3.B Peripheral Vascular Disease--Atomic Energy Commission

In FY 72, AEC conducted three programs related to peripheral vascular disease:

- Biomaterials. The Atomic Energy Commission's Division of Applied Technology funds and administers contract supported research on blood-compatible materials for prosthetic use in the vascular system (FY 72: two offsite contracts, totalling $140,000). This effort consists of synthetic work on new polymeric substances.

- Aging and the Peripheral Vasculature. The AEC funds and administers contract supported studies in this area (FY 72: three onsite contracts, totalling $320,000). Investigators at the University of Rochester are studying morphologic, biochemical, and functional changes occurring in the peripheral vasculature as a consequence of aging. Cell death and fibrotic changes (fibroatrophy) appear to occur progressively with consequent impairment of exchange of materials between the vascular compartment and parenchymal cells of body tissues. Experimental evidence suggests that the degenerative changes underlying fibroatrophy are accelerated by ionizing radiation. Research at the Argonne National Laboratory is concerned with effects of aging and radiation on the microvasculature. Detailed micropathology and techniques of nuclear medicine are used to correlate localized damage with capillary function and regeneration.

- Radiation Effect on Capillaries and Functional Stromal Cells. At the University of California (San Francisco), radiation effect on capillaries and functional stromal cells are being studied both qualitatively (by electronmicroscopy) and quantitatively (LDV 50 end points) in mouse and rat tissues. Repair of radiation damage is also being evaluated, as is the effectiveness of protective and sensitizing agents in modifying the radiation response.

In addition, see description of nuclear medicine research presented in Section 1.2.B.

1.3.C Peripheral Vascular Disease--Department of Defense

In FY 72, the Department of the Air Force conducted on study related to peripheral vascular disease:

- Survey of lipid and lipoprotein factors and investigation into newer modes of treatment in patients with arteriosclerotic peripheral vascular disease (funded with operating resources).

1.3.D Peripheral Vascular Disease--Environmental Protection Agency

No identified ongoing EPA research is directly related to this area.

1.3.E Peripheral Vascular Disease--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

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No identified ongoing EPA research is directly related to this area.

1.3.E Peripheral Vascular Disease--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

1.3.F Peripheral Vascular Disease--Health Services and Mental Health Administration

No identified ongoing HSMHA supported research activities are related directly to this area.

1.3.G Peripheral Vascular Disease--National Aeronautics and Space Administration

The Biomedical Research Division, NASA, funds and administers an in-house study (FY 72: $28,000) entitled "Control of Vascular Distensibility." The response of the peripheral cardiovascular system, particularly the veins, is being studied by biophysical methods to determine the significance of the capacitance venous system in the altered orthostatic tolerance seen universally after weightlessness and bedrest (weightlessness analog). Studies are directed towards the determination of the mechanical properties of the heart and great veins during test and subsequent pharmacologic stimulation to determine methods for detection of such properties by noninvasive methods (ultrasound). Methods are also presently being evaluated to determine central venous pressure by such noninvasive means.

Specifically:

- The mechanical properties of the heart and great veins are being studied by biophysical methods which include the determination of pressure circumference relationships and wave speed propagation. Actual and theoretical analyses of resultant data are being used in appropriate models to arrive at the material properties of selected structures.

- Noninvasive (ultrasonic) methods are being used and evaluated for obtaining identical data based primarily on wave speed characteristics from two transcutaneous flowmeters placed at known distances on the same structure.

- Central venous pressure is being evaluated noninvasively as the intrathoracic pressure required to impede peripheral venous flow detected transcutaneously.

For additional description of NASA studies related to peripheral vascular disease, see Sections 1.2.G (diagnostics), 1.4.G (project entitled "Advanced Cardiovascular Measurement Techniques"), and 1.10.G ("Effects of Space Flight on Vascular Permeability").

1.3.H Peripheral Vascular Disease--National Science Foundation

For description of NSF supported research activities related to this area, see Section (5) 1.1.H and 1.2.H.

1.3.I Peripheral Vascular Disease--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitative activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

1.3.J Peripheral Vascular Disease--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

1.3.K Peripheral Vascular Disease--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

1.3.L Peripheral Vascular Disease--Veterans Administration

The VA funds, conducts and/or administers a number of studies related to peripheral vascular disease. (No information on FY 72 funding was available for this report.) The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics. These studies include:

- The Relationship of Zinc to Peripheral Vascular Disease. A clinical study in 1966 indicated that zinc deficiency appeared to be a factor in the production of atherosclerosis. It reported zinc sulfate therapy as being of symptomatic benefit in patients with obliterative vascular disease of the lower extremeties. The present study was devised to determine whether there is any relationship between the level of serum zinc and the level of zinc and lipids in the aorta. The study has shown to date that there is no significant relationship between the levels of zinc in the serum and in aortic ash. The amount of zinc in the aortic ash is inversely correlated with the degree of aortic atherosclerosis.

There is no relationship between the level of serum zinc and degree of atherosclerosis. The clinical finding that serum zinc deficiency appears to be a factor in the production of atherosclerosis thus is not explained.

- Radioisotope Imaging--(Diagnostic Procedures). Coronary arteriography satisfactorily delineates obstructive lesions of the major coronary arteries, but does not yield information regarding myocardial perfusion. Hence small vessel disease or branch vessels with total orifice obstruction may be missed and the flow through partially obstructed vessels may be overestimated. Radioisotope imaging, after intra-coronary artery injections of labeled microspheres, properly sized to allow distribution to follow blood flow but too large to pass through capillaries, should allow an estimate of regional myocardial perfusion to be made.

  An evaluation of this technique in dogs has been completed. Excellent images were obtained with a total dose of microspheres less than 1/50 of that needed to cause hemodynamic changes. No histological or laboratory evidence of myocardial damage was found.

  Subsequently, an IND application was approved and a study has been undertaken of 23 patients who were undergoing diagnostic coronary arteriography. The experience to date indicates that the method is safe and suggests that it will be a useful tool for evaluating myocardial blood flow, particularly in patients where surgical intervention is contemplated.

- Significance of Pulsatile Blood Flow Waveforms in Peripheral Vascular Surgery. This ongoing research program includes the following individual research projects:

  - A study of the hemodynamics of pulsatile blood flow in peripheral vascular disease before, during, and after direct arterial surgery and/or lumbar sympathectomy.

  - An assessment of vascular status of patients pre- and post-operatively by noninvasive flowmetry technique.

NHLI

- Comparison of pulsatile blood flow waveform detected by electromagnetic flowmetry with the waveforms obtained by impedance plethysmography and ultrasonic flowmetry (from this the significance of the various parameters of pulsatile flow is becoming evident).

- Responses of denervated vessels to specific vasodilators (which provides information as to the efficacy of specific vasodilators for treatment of peripheral vascular disease.

- Use of transthoracic impedance plethysmography (which has provided a means for detecting deep vein thrombosis and pulmonary edema).

- The use of simultaneous bilateral multipoint skin surfact temperature measurements (this is part of a vascular evaluation and has provided an informative adjunct to flowmetry measurements).

For additional information on studies by the VA relevant to peripheral vascular disease, see Sections 1.1.L and 1.2.L.

1.4 HYPERTENSION

1.4.A Hypertension--Department of Agriculture

The USDA funds and administers/or conducts research related to this area (FY 72: three projects, no funding data available):

- An Investigation of the Effect of Diet on Blood Pressure. The objectives of this study are:
  - To determine the effects of individual dietary components upon the development of elevated arterial blood pressure and alteration of renal structure;
  - To analyze organic and mineral components of the diet which cause elevated blood pressure and renal pathology;
  - To determine the sequence and causation of these diet-induced results.
- An Investigation of Blood Regulation in Chickens. The objectives of this study are to:
  - Determine the role of catecholamines, serotonin and histomine (and their inhibitors); on blood pressure and cardiac output in birds; and
  - Determine the role of the thymus and bursa of Fabricius on the level and release of serotonin.
- An Investigation of the Influence of Dietary Sodium upon Blood Pressure of the Pregnant Rat and Progeny. The objectives of this study are:
  - To determine the relationship between the level of sodium intake during pregnancy and maternal blood pressure;
  - To establish the relationships among blood pressure and indices of renin and aldosterone secretion; and
  - To determine whether a relationship exists between sodium intake during pregnancy and lactation and the blood pressure of the progeny.

NHLI

1.4.B Hypertension--Atomic Energy Commission

The AEC funds and administers contract-supported studies in hypertension (FY 72: three onsite contracts, totalling $540,000):

- A sizable research activity at the Brookhaven National Laboratory seeks to identify and characterize genetic factors underlying hypertension. Studies with rats have demonstrated that multiple genetic factors predispose an individual to hypertension. Current studies are elucidating gene-controlled metabolic processes (18-hydroxylation of steroids in the adrenal cortex, factors involved in the renin-angiotensin system, and cholesterol metabolism) that contribute to the etiology of hypertension. Clinical research is concerned with the study of possible genetic interrelationships between hypertension, obesity, diabetes, gout, and atherosclerosis. Hypertension research at the Brookhaven facility is also supported by funds from NHLI (FY 72: two grants, totalling $60,000).

- Radiation-induced renal hypertension is under study at the University of Rochester. Secondary pathologic effects of hypertension in organs such as spleen and liver are being investigated.

- Investigators at Brookhaven National Laboratory are studying brain proteases that degrade peptide hormones, including the bradykinins.

The AEC-NHLI (jointly funded) Epidemiological Study of Coronary Heart Disease, Cerebrovascular Disease and Hypertension in Hiroshima, Nagasaki, Hawaii, and San Francisco is related to this area. (See Section 1.2.B, Coronary Heart Disease, for topic description.)

Also related to this area is the AEC supported research on biochemical correlates of experimental cardiac hypertrophy (see Section 1.8.B, Cardiomyopathy).

1.4.C Hypertension--Department of Defense

No identified ongoing DOD research is directly related to this area.

1.4.D Hypertension--Environmental Protection Agency

No identified ongoing EPA research is directly related to this area.

1.4.E Hypertension--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

1.4.F Hypertension--Health Services and Mental Health Administration

The NIMH, HSMHA, funds and administers research related to the area of hypertension.

Among these NIMH supported research projects are:

- Experimental Studies of Long-Term Stress
  (See Section 1.2.F on Coronary Heart Disease for topic description.)
- Instrumental Learning of Cardiovascular Responses
  (See Section 1.2.F on Coronary Heart Disease for topic description.)

NHLI

The Regional Medical Programs Service (RMPS), HSMHA, funds and administers programs in this area (FY 72: 10 projects totalling $1,127,723).

These projects include:

- Intermountain RMP #46: Curable Hypertension Identification Program (FY 72: one project totalling $12,923). This project is designed:

  - To provide service facilities where practicing physicians can obtain laboratory data essential to the diagnosis and treatment;

  - To create awareness among physicians as to the possible presence of metabolic and endocrine abnormalities; and

  - To derive statistical information.

  Three laboratories, an immunoassay, a chemical to measure steroid hormones and a developmental to refine techniques, were established. Abnormal finds to be reported to the referring physician by phone by an M.D. competent to offer consultation. Educational programs are designed for each physician using the laboratory determination as a stimulus and point of entry.

- Missouri RMP #46 and 46A: High Blood Screening and Treatment (FY 72: one project, totalling $169,851). This project is designed to attack the problem of disability and death from strokes and cardiovascular disease secondary to hypertension in a predominately Negro area of Kansas City by demonstrating that hypertension in the early stages can be controlled.

- Metropolitan D.C. RMP #42: Establishment of Selected Hypertension Clinics in Economically Depressed Areas (FY 72: one project, totalling $22,050). This project is designed to improve the health care of patients with hypertension within metropolitan Washington, D.C. by establishing a reference and control center tying together five clinics: District of Columbia General Hospital, Washington Hospital Center, Anacostia Neighborhood Clinic, Freeman's Hospital and Columbia Hospital for Women. (Paramedical personnel have been trained to record blood pressures and to determine that the management plan is being followed.)

- Illinois RMP #18: Computerized Hypertensive Treatment (FY 72: one project, totalling $118,535). This project is designed to develop a computerized form of logic for evaluation and care of hypertensives which could be applied to massive community programs.

- Georgia RMP #27: Community Hypertension Program (project #27) (FY 72: one project, totalling $133,333). This project is designed to uncover factors that deter indigent patients from seeking medical care for hypertension and to develop methods for motivating them to seek and accept medical care.

- Georgia RMP #32: Stroke Area Facilities (FY 72: $53,976). This project is designed to help hospitals with strong hypertension and stroke programs provide outreach to train staffs in smaller hospitals in the region in hypertension management and stroke care.

- Mississipi RMP #32: Hypertension Control Program (FY 72: one project, totalling $9,131). This project is designed to screen the population of Sharkey and Issaquena counties, two of the most rural, sparsely populated low income counties in Mississippi in an effort to determine the incidence of hypertension. Diagnosis, treatment and follow-up of hypertensive patients is provided by the health department, the sponsoring agency, with assistance from the local medical personnel and the University Medical Center.

- Memphis RMP #40: Hypertension Control Program (FY 72: one project, totalling $42,651). This project is designed to develop a model demonstration hypertension control program for selected county health departments in north Mississippi to:

  - Demonstrate the ability of public health nurses and allied health personnel to conduct a hypertension screening and control program with a minimum of M.D. support;

  - Create and increase awareness of the general public to hypertension and its complications to the point of seeking care;

  - Provide resources for medical care at the local level for the majority of the medically indigent hypertensives; and

  - Assure continuity of care for the hypertensive.

- Tennessee Mid-South RMP #48: Regional Program for the Improved Control of Hypertension (FY 72: one project, totalling $115,401). This project is designed to improve the care of hypertensive patients by two means:

  - Continuing education in the diagnosis and management of patients with hypertension;

  - Follow-up after the patient has been diagnosed and treated.

- Tennessee Mid-South RMP #57: Alton Park Health Center Demonstration Project (FY 72: one project, totalling $93,333). This project is designed to demonstrate in a defined population of hypertensive patients the feasibility of long-term follow-up hypertensive patients using largely the services of nurses.

- New York/Metropolitan RMP #17: Harlem Region Stroke and Hypertension Program (FY 72: one project, totalling $356,539). This program demonstrates hypertension screening, diagnosis, treatment and follow-up as well as optimum stroke care and rehabilitation for a major part of Harlem.

1.4.G Hypertension--National Aeronautics and Space Administration

The Biomedical Research Division, NASA, funds and administers both in-house and contract-supported studies in this area.

Among these studies (which primarily deal with fluid and electrolyte balance, and volume regulation) are:

- Hormonal Control of Fluid and Electrolyte Metabolism. (In-house study, FY 72: $50,000). The objectives of this study are:
  - To measure the plasma levels of renin, angiotensin, converting enzyme, and aldosterone in man subjected to blood volume redistribution induced by tilt table stress, prolonged bedrest and/or appropriate centrifugation profiles. Lower animals are being used as test subjects where indicated.
  - To improve sensitivity and specificity of radioimmunoassays for ADH and angiotensin.
  - To devise sensitive kinetic methods for assaying renin, the converting enzyme and angiotensinases in human and animal plasmas.

  NOTE: Exposure to weightlessness appears to produce a reduction of plasma volume in humans which may be caused by changes in activity of the renin-angiotensin system and by changes in ADH and aldosterone levels. An accurate assessment of the response of these hormones is needed to establish the role of these hormones in blood volume reduction produced by variations in "g" force.

- A Study of the Kinetics and Physiologic Role of the Vasoactive Hormones (FY 72: one contract totalling $25,000). This study was designed to evaluate long-term adaptive mechanisms which are likely to be affected by long-duration manned space missions. It has necessitated and been predicated upon development of reliable assays based on feasible methodology (i.e., radioimmunoassay) applicable to space activities.

NHLI

Practical value from such techniques is achieved by fullest understanding of actual physiochemical pathways involved in the vasoactive hormones under study. Specific emphasis has been placed on the role of these hormones in orthostatic hypotension.

- The Effects of Atrial Distension on Salt and Water Excretion (FY 72: one contract, totalling $23,000). This project is designed to study the effect of atrial distension on the kidney's salt and water absorption and excretion. Maintenance of extracellular fluid volume and effective circulating vascular volume are essential to normal function of the organism. Mechanisms achieving homeostasis of this aspect of cardiovascular-renal dynamics are poorly understood and conflicting in explanation. These investigators propose some relatively definitive studies to clarify the specific role of atrial distension in these physiologic control responses.

  Rates of Na+ and water reabsorption in three segments of the rat cortical nephron are being determined by micropuncture technique prior to, during, and after atrial distension under at least four conditions: hydropenia, water loading, salt and water loading, and during intravenous saline extracellular volume expansion. Atrial distension by ligature and/or balloon catheter is also being tried. Appropriate cadiodynamics (pressure, flow, volume) are being monitored during tests.

- Role of Systemic and Renal Hemodynamics as Determinants of Sodium Excretion and Volume Regulation (FY 72: one contract, totalling $25,000). The ultimate objective of this study is to systematically investigate and define the complicated relationships between systemic and renal hemodynamics, renal sodium regulation and extracellular volume control. These efforts are directed at better understanding changes which occur during prolonged space flight such as orthostatic intolerance, decreased body water, and cardiovascular deconditioning.

A multifaceted experimental approach is being followed:

- Investigation on dogs of certain "volume receptors" which control sodium reabsorption and excretion

- Evaluation of adrenergic effect on sodium reabsorption and excretion

- Investigation of relationships between hemodynamically induced changes in sodium excretion and renal oxygen consumption

- Study of the role of redistribution of glomerular filtrate in the natriuretic response to volume expansion

- Investigation of the role of proximal tubular reabsorption in the control of renin release.

Progress: Systematic investigation into the role of intrarenal hemodynamics as a regulator of extracellular volume has demonstrated that--

- Natriuresis after volume expansion is closely related to renal blood flow.

- Renal vasodilation without volume expansion increases sodium excretion.

- Increased arterial pressure decreases sodium reabsorption if pressure is transmitted along intrarenal circulation secondary to vasodilation.

- Effects of Altered Gravitational Stress on Fluid Balance and the Circulation of Blood (FY 72: one contract, totalling $48,000). The objectives of this study are:

  - To devise a mathematical model of the volume and distribution of blood together with changes in arterial pressure, cardiac output and regional blood flow during postural shifts utilizing data from the literature

- To study the control of the renal circulation and excretion of sodium and water during tilting and bedrest

- To study the long-term regulation of sodium and water balance as influenced by the changing volume and distribution of blood, first during bedrest and then under weightlessness.

This study is designed to identify certain principal physiological control mechanisms which determine the effects of postural shifts and weightlessness on circulation, renal function, and endocrine factors controlling sodium and water balance. This task focuses particularly on the endocrine factors influencing blood volume and distribution and the control of arterial pressure. (The results of these studies will be applied to the design of remedial garments, rehydration procedures, etc., to help counteract the deleterious effects of Space Shuttle reentry G-forces. These studies will provide ground-based data.)

1.4.H Hypertension--National Science Foundation

The FY 72 the NSF funded and administered four programs (FY 72 funding, $93,700) directed at developing an understanding of biological control mechanisms.

- Endocrine Factors Associated with Water and Electrolyte Metabolism in Birds. Studies are continued on the metabolism of corticosterone and aldosterone in mature and developing intact ducks and in acutely and chronically adenohypophysectomized ducks.

  An elucidation of the chemical nature and the physiological significance of the circulating and excreted metabolites of the adrenocortical steroids is emphasized. Through the use of replacement therapy in adenohypophysectomized ducks, the mechanisms associated with the control of hormone metabolism will be examined.

Samples of kidney, spleen, lung, reproductive tract, testis and adrenal glands will be extracted and analyzed for the presence of prostaglandins. The occurrence of PGE_2, and possibly PGA_2, in kidney tissue will be examined in ducks maintained on freshwater and during their adaptation to seawater. Attempts will be made to explain the normotensive state maintained by the duck during adaptation to seawater.

- Control of Renal Hormones. It has been demonstrated previously that angiotensin stimulates ADH secretion. Work is directed at defining this relation more precisely. A series of experiments are being conducted which are known to alter either ADH or renin levels, and both hormones will be cultured in blood. Additional experiments will be done on anephric animals, in which the renin response is eliminated in order to determine in which situations ADH changes are secondary to renin changes. Experiments will include altering left atrial pressure by inflation of a balloon in the atrium, altered diets (NaCl), changing posture, and hemorrhage. It is also proposed to incubate posterior pituitary glands alone, and ones still attached by the stalk to the hypothalamus. The effect of various salts, drugs and hormones on ADH release in these preparations are being studied so as to get at their site of action.

- Renin Secretion in Rats. The two broad objectives of the proposed research are to measure rates of renal renin secretion into the blood, in anesthetized rats; and, to discover if, as current research suggests, renin secretion is controlled by either the concentration of sodium in, or the mass of sodium delivered to, the early distal tubules in the kidney. Renin secretory rates (the product of renal plasma flow and renal venous minus arterial reference in plasma renin activity) are to be measured in normal rats as well as in chronically sodium deprived and sodium loaded rats, and in normal rats before and after induction of mannitol and saline diureses. These experiments are to define some situations during which renin secretion is chronically and acutely changed from control secretory rate. Then, using standard micropuncture techniques, distal tubule sodium concentration and sodium load (mass of sodium/minute delivered to the

early distal tubule) will be measured in other, but identically treated, rats; that is, in normals before and during diuresis, and in chronically sodium deprived and sodium loaded rats. If renin secretion depends upon distal sodium concentration or upon load, one of these two variables should change in a manner consistent with the renin secretion data.

- Renal Function and Blood Flow Distribution in Marmots. Studies are being performed on marmots of both sexes to determine in awake and hibernating animals: seasonal variations of renal function and urinary concentrating ability; blood flow distribution to selected areas and associated vascular resistance; extracellular space, total body water and volumes of distribution of creatinine and PAH; and, the responsiveness to hormones, specifically those that influence water and electrolyte balance; ADH and aldosterone.

1.4.I Hypertension--Social and Rehabilitation Service

No identified ongoing SRS supported research or rehabilitation activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

1.4.J Hypertension--Social Security Administration

No identified ongoing SSA supported research activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

1.4.K Hypertension--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

1.4.L Hypertension--Veterans Administration

The VA funds conducts and/or administers a number of studies related to hypertension. (No information on FY 72 funding was available for this report. The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics.) These studies include:

- Veterans Administration Cooperative Studies on Hypertension. The report of the VA Cooperative Study on Antihypertensive Agents (JAMA August 17, 1970) demonstrated that drug treatment is effective in the prevention of major heart, kidney, brain and blood vessel complications in moderate hypertension. This study has significant implications for the 23 million persons in the United States with elevated blood pressure. Their risk of developing strokes, heart failure and kidney failure is far higher than in the normal population. The VA trial represented a milestone in medicine by demonstrating that these complications are preventable by treatment.

  A report in May 1972, presented a further analysis of the results of the study. In this report the risk of complications and benefit of treatment was evaluated against the patient's age, level of blood pressure and presence of cardiovascular damage. It was shown that treatment was effective at any age or in the presence of damage. The higher the level of blood pressure the more

definite were the benefits of treatment. Side effects produced by the drugs also were analyzed in detail. The side effects were of minimal significance compared to the benefits derived from treatment.

Several new studies being initiated in FY 72 include:

- Comparative Study of Bethanidine vs. Guanethidine. A comparative clinical trial study of Bethanidine vs. Guanethidine in the treatment of patients with diastolic blood pressure 100-129 mm. of Hg. while on hydrochlorothiazide is being conducted. The objectives of this study are:

  - Comparative short term antihypertensive effectiveness of Bethanidine and Guanethidine when used together with hydroclorothiazide as measured by the percentage of patients in each group who exhibited a blood pressure of below 90 mm Hg, by the comparison of differences of BP response in the two groups, by comparison of intrapatient diurnal variation of blood pressure in each group determined on basis of home blood pressure, and by comparison of the intrapatient diurnal variation of BP in each group determined on basis of blood pressure check during a 24-hour period of hospitalization at the sixth month of the postrandomization period;

  - If Bethanidine measures up to Guanethidine for a six month period, the study will be extended to two years for further comparison; and

  - Comparative frequency of side effects are to be made.

- Efficacy of Propranolol in Hypertensive Patients with Diastolic Pressures Less than 110 mm Hg and Evaluation of Systolic Time Intervals. The objectives of this study are:

- To determine whether or not propranolol alone, titrated by increments of 40 mg t.i.d. monthly to a maximum dose of 160 mg t.i.d., will reduce arterial blood pressure as effectively as the commonly used medication combination of reserpine and hydrochlorothiazide;

- To determine whether or not the antihypertensive effect of propranolol is enhanced by the addition of hydrocholrothiadize and/or hydralazine to the point that blood pressure reduction is comparable to that achieved by the commonly used combination of reserpine and hydrochlorothiazide; and

- To determine whether or not incidence, severity, and gravity of side effects on treatment with propranolol, or propranolol plus hydrochlorothiazide, or plus hydralazine and hydrochlorothiazide, are less than on treatment with reserpine and hydrochlorothiazide.

- Effect of Withdrawing Active Treatment on Blood Pressure in Patients on Antihypertensive Drugs for Two Years or Longer. This study was started in January 1971 to determine the feasibility of discontinuing antihypertensive therapy in those patients who have been on antihypertensive agents for the last two years and well-controlled for at least one year. This possibility had been suggested previously by investigators, experimentally and in retrospective studies, but results have been contradictory. The possibility that downward resetting of baroceptors might occur in some hypertensive patients on prolonged drug treatment, and thereby eliminate the need for drug therapy, would be of great importance if found to be true. Aside from the obvious convenience for the patient, it would avoid undesirable side reactions of drugs used in treatment, as well as eliminate the cost of medication which would be considerable when one considers the number of years the patient would be on active drug therapy.

NHLI

This study is part of a national cooperative study on antihypertensive agents being carried out in seventeen (17) participating VA Hospitals (and is scheduled for completion in FY 73).

- Angiotensin--Aldosterone Interrelationships. This major project has been an ongoing attempt to clarify interrelationships of substances which may be important in the genesis of hypertension. Attempts have been made to use an animal model in which specific antibodies to angiotensin have been raised to nullify angiotensin's effects and then to stimulate aldosterone production by other means. Also, manipulations of the kidney have been carried out and levels of aniotensin and aldosterone measured. The manipulations include nephrectomy and tying off a renal artery, renal vein, and ureter.

- Renin and Hypertension. The cause of benign essential hypertension (high blood pressure) in man continues to be a subject of speculation. Research has suggested two possible causes: production of excess renin by the kidney and production of excess norephinephrine by the sympathetic nervous system. Both of these compounds help to maintain blood pressure normally. The VA is addressing the problem of what elevates blood pressure abnormally in hypertension.

  VA studies have recently confirmed reports of persons with long-term "essential hypertension" do not have an increased amount of renin in the blood although persons with acute malignant hypertension do. It has also shown that in experimental animals with chronic renal hypertension the injection of a renin-inactivating serum lowers the blood pressure only after a considerable delay. These findings suggest that perhaps in some forms of hypertension normal or elevated amounts of renin are secreted by the kidney, but that the amount in the blood is lower than normal because it is being rapidly extracted by the artery wall (where renin acts) and stored therein.

- In one study to test whether increased extraction and storage of renin may actually occur, renin was infused into rats for 30 minutes. The major arteries were removed 15 or 30 minutes later and their renin content assayed. Also blood samples were taken immediately before and after the infusion and after the non-infusion waiting period immediately before tne removal of the artery. These, too, were analyzed for renin content. Similar control experiments were done substituting simple salt solution for renin. Preliminary results have shown that about half of the rats given renin accumulated greater amounts of this substance in their artery wall than was found in control rates given saline. However, in those animals with high accumulation, the blood content of renin tended to be increased even before this material was infused. Hence, the question as to whether infused renin passes into the artery wall is not yet resolved.

- Another study being done is concerned with the hypertension which occurs spontaneously in a certain strain of rats and which appears to resemble human "essential hypertension." In the animals studied to date the blood renin level was lower than normal but renin in the arterial wall was increased. This is consistent with the hypothesis that in the human counterpart of rat spontaneous hypertension, although blood renin is low, arterial renin might be high.

- Hemodynamic Factors in Renin Release and Model of Unilateral Renovascular Hypertension in Dogs. In this study, designed to elucidate the factors leading to renin release and thus to renovascular hypertension, an experimental model has been developed in which hemodynamic factors to a perfused kidney can be controlled and changed individually; i.e.,..flow, mean pressure and presence or absence of pulsation. By direct renal vein cannulation venous samples can be obtained at each experimental point and thus the factor or factors triggering renin release can be more accurately determined. Early results suggest a

NHLI

direct relationship between renin output and change in mean pressure. There also appears to be an inverse relationship between the renin output of the two kidneys i.e.,..as renin output of the experimental kidney increases renin output of the opposite or nonexperimental kidney decreases.

- Study of Personality Patterns in Essential Hypertension. This study is based on the hypothesis that in order for the physician to provide effective treatment to the hypertensive patient, a knowledge of the patient's personality features, is extremely helpful.

  This study has involved 40 patients, 20 with a diagnosis of essential hypertension and 20 other illnesses. All were administered through well-accepted psychological tests. Preliminary indications are that the essential hypertensive patients are more dependent and more concerned about closer affiliation with others. They seem to be less aggressive and less dominant than the other group of patients and generally display evidence of a lower self-esteem.

1.5 STROKE

1.5.A Stroke--Department of Agriculture

No identified ongoing research of the USDA is directly related to this area.

1.5.B Stroke--Atomic Energy Commission

Three AEC supported efforts relate to stroke:

- Epidemiological Study of Coronary Heart Disease, Cerebrovascular Disease and Hypertension in Hiroshima, Nagasaki, Hawaii and San Francisco. (See Section 1.2.B on Coronary Heart Disease for topic description.)
- AEC sponsored research in hypertension. (See section on Hypertension for topic description.)
- AEC supported research on nuclear medicine technology. (See Section 1.2.B--Coronary Heart Disease for description.)

1.5.C Stroke--Department of Defense

No identified ongoing programs of the DOD are directly related to this area.

1.5.D Stroke--Environmental Protection Agency

No identified ongoing programs of EPA relate directly to this area.

1.5.E Stroke--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and

testing of new drugs which may be used in research and treatment in this area.

1.5.F Stroke--Health Services and Mental Health Administration

The Regional Medical Program Service (RMPS), HSMHA, is supporting a contract with the Joint Committee on Stroke Facilities through the American Neurological Association to develop guidelines in the field of stroke. The level of support in FY 72 was approximately $150,000.

In addition, RMPS funds and administers the following programs in this area (Total FY 72: 56 Programs, $3,199,178--no descriptions of these projects were available at time of report preparation):

- Alabama RMP #28: Production Audiovisual Materials Orientation (FY 72: One Project, $47,783)
- Arkansas RMP #52: Rehabilitation and Comprehensive Care (FY 72: Three Projects, $31,073)
- Bi-State RMP #56: Comprehensive Diagnosis, Intensive Care and Rehabilitation (FY 72: Four Projects, $108,661)
- California RMP #19: Comprehensive Stroke Program (FY 72: Five Projects, $718,863)
- Connecticut RMP #08: Stroke Prognosis (FY 72: One Project $30,000)
- Metropolitan RMP #31: Freedmens Hospital Stroke Program (FY 72: One Project, $39,510)
- Georgia RMP #46: Stroke Area Facilities (FY 72: One Project, $53,976)
- Intermount RMP #15: Model Stroke Demonstration (FY 72: One Project, $60,560)

- Indiana RMP #43: Regional Stroke Program (FY 72: One Project, $114,153)
- Iowa RMP #27: Stroke Management Project (FY 72: One Project, $68,000)
- Louisiana RMP #33: Discharge Planning Program (FY 72: One Project, $59,666)
- Maryland RMP #44: Neurological Training and Model (FY 72: Two Projects, $27,000)
- Memphis RMP #51: Stroke Project (FY 72: One Project, $8,414)
- Michigan RMP #53: Demonstration, Education, Comprehensive Care (FY 72: Five Projects, $470,691)
- Mississippi RMP #57: Stroke Care Demonstration and Training (FY 72: One Project, $121,952)
- Missouri RMP #09: Prevention and Mobile Rehabilitation (FY 72: Two Projects, $68,900)
- Nassau-SFK RMP #66: Stroke Evaluation and Referral (FY 72: One Project, $50,000)
- New Jersey RMP #42: Comprehensive Care and Education (FY 72: Two Projects, $54,200)
- New Mexico RMP #34: Stroke Program (FY 72: One Project, $89,432)
- New York City Metro RMP #58: Hemiplegia Registry (FY 72: One Project, $55,872)
- North Carolina RMP #06: Comprehensive Stroke Program (FY 72: One Project, $124,070)
- North Dakota RMP #60: Training Nurses in Rehabilitation Techniques (FY 72: One Project, $24,071)
- Northeast Ohio RMP #64: Rehabilitation Demonstration (FY 72 One Project, $89,260)
- Ohio State RMP #22: Rehabilitation Training Project for Health Professions (FY 72: One Project, $33,952)

NHLI

- Oregon RMP #12: Community Stroke Rehabilitation Program (FY 72: One Project, $22,085)
- Puerto Rico RMP #65: Guaynabo Stroke Prevention Program (FY 72: One Project, $124,728)
- Rochester RMP #25: Neurologic and Rehabilitative Nursing (FY 72: One Project, $8,957)
- South Carolina RMP #35: USC Stroke Nurse Training (FY 72: One Project, $15,000)
- Tennessee-Mid State RMP #18: Speech Rehabilitation Program for Aphasics and Laryngectomees (FY 72: One Project, $3,000)
- Texas RMP #07: Demonstration, Rehabilitation Management and Techniques (FY 72: Five Projects, $186,270)
- Tri-State RMP #62: Care and Regional Center (FY 72: Two Projects, $138,908)
- Virginia RMP #49: Stroke in a Small Rural Community (FY 72: One Project, $39,166)
- Washington-Alaska RMP #38: Stroke Nursing Techniques (FY 72: Three Projects, $111,005)

1.5.G Stroke--National Aeronautics and Space Administration

For description of NASA programs related to stroke, see Section 1.2.G (diagnostics) and 1.10.G ("Effects of Space Flight and Vascular Permeability").

1.5.H Stroke--National Science Foundation

In FY 72 the NSF funded and administered one program (FY 72 funding: $22,850)directed at developing more knowledge on nonlinear pressure-volume relationship with an aneurysm.

Various physical models of saccular aneurysms of the Circle of Willis provide evidence of a nonlinear pressure-volume relationship within the aneurysm. This investigation has to date resulted in the development of an electric analogue of the model aneurysm which emphasizes the importance of further studies on pressure and flow relations in the blood vessels entering and those comprising the Circle of Willis. A variety of experiments using dogs, monkeys and patients is being conducted to further develop information regarding pressure and flow relations and the general cerebrovascular dynamics of the Circle of Willis.

1.5.I Stroke--Social and Rehabilitation Service

The SRS provides third party payments for provision of care (which may involve participation in clinical research). The SRS also funded and administered one project in FY 72 related to this area.

- Parameters of Ischemic Cerebrovascular Disease Relative to Rehabilitation. A study to determine causative factors of ischemic cerebrovascular disease and its natural course. (FY 72: $125,000).

1.5.J Stroke--Social Security Administration

No identified ongoing SSA supported research activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

NHLI

1.5.K Stroke--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

1.5.L Stroke--Veterans Administration

For discussion of studies relevant to stroke, see Sections 1.2.L and 1.4.L.

1.6 CONGENITAL HEART DISEASE

1.6.A Congenital Heart Disease--Department of Agriculture (USDA)

No identified ongoing USDA supported efforts relate directly to this area.

1.6.B Congenital Heart Disease--Atomic Energy Commission

No identified ongoing AEC supported work is directly concerned with this area.

1.6.C Congenital Heart Disease--Department of Defense

No identified ongoing DOD supported efforts related directly to this area.

1.6.D Congenital Heart Disease--Environmental Protection Agency

The Community Health and Environmental Surveillance Studies (CHESS) of the Human Studies Laboratory of EPA (See Section 2.2.D for description of CHESS) includes analyses of the affects of atmospheric pollution on persons with chronic heart diseases.

1.6.E Congenital Heart Disease--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

1.6.F Congenital Heart Disease--Health Services and Mental Health Administration

The Maternal and Child Health Service, HSMHA, supports Regional Congenital Heart Centers for care of children with congenital heart disease (FY 72: $732,000). Note: of this amount $180,000 is for the New England Infant Cardiac Program, which involves the cooperation of 11 hospitals.

The Regional Medical Programs Service funded and administered six projects (FY 72: $281,035) directed at pediatric cardiac screening and clinical services.

Under the RMPS contract with the American Heart Association for the support of the Intersociety Commission on Heart Disease Resources, the following guideline reports which discuss various aspects of congenital heart disease are being updated:

- Primary Prevention of Congenital Heart Disease
- Resources for Optimal Acute Care of Patients with Congenital Heart Disease
- Optimal Radiologic Facilities for Examination of the Chest and Cardiovascular System
- Resources for Optimal Long-Term Care of Congenital Heart Disease
- Optimal Resources for Cardiac Surgery (FY 72 funding is presented in Section 1.1.F).

1.6.G Congenital Heart Disease--National Aeronautics and Space Administration

For description of NASA activities related to congenital heart disease, see Section 1.2.G.

1.6.H Congenital Heart Disease--National Science Foundation

For description of related research supported by NSF (Blood Flow Past Aortic Heart Valves) see Section 1.7.H.

1.6.I Congenital Heart Disease--Social and Rehabilitation Service

One project funded and administered by SRS and listed in Section 1.2.L (Coronary Heart Disease) is applicable to Congenital Heart Disease, i.e., "Critical Selection of Heart Surgery Patients for Vocational Rehabilitation." The SRS provides third party payments for provision of care (which may involve participation in clinical research).

1.6.J Congenital Heart Disease--Social Security Administration

No identified ongoing SSA supported activities related directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

1.6.K Congenital Heart Disease--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

1.6.L Congenital Heart Disease--Veterans Administration

The VA conducts one identified study related to congenital heart disease (no information relative to the source or type of support mechanism or FY 72 funding was available at the time this report was prepared). This study was:

- Design and Testing of Artificial Heart Valves. This project involves the design and testing of a new artificial valve for replacement of the mitral and tricuspid valves. This valve has already been shown to be effective in dogs up to several months after implantation. It has the advantages of a central flow pathway, a flexible ring, and a cuspid structure--none of which the orthodox prostheses have. Work is more centered on optimal design, flow and fatigue characteristics, and nature of materials.

See Section 1.2.L for additional information on VA studies relevant to congenital heart disease.

1.7 RHEUMATIC AND OTHER VALVULAR HEART DISEASES

1.7.A Rheumatic and Other Valvular Heart Diseases--Department of Agriculture

No identified ongoing USDA research relates directly to this area.

1.7.B Rheumatic and Other Valvular Heart Diseases--Atomic Energy Commission

See AEC supported research on experimental methods (involving scintillation scanning) of detecting atrial thrombi that are secondary to mitral valve disease (see Section 3.2.B, Arterial Thromboembolism).

1.7.C Rheumatic and Other Valvular Heart Diseases--Department of Defense

No identified ongoing DOD supported activities relate directly to this area.

1.7.D Rheumatic and Other Valvular Heart Diseases--Environmental Protection Agency

The Community Health and Environmental Surveillance Studies (CHESS) of the Human Studies Laboratory of EPA (see Section 2.2.D for description of CHESS) includes analyses of the effects of atmospheric pollution on persons with chronic heart diseases.

1.7.E Rheumatic and Other Valvular Heart Diseases--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

1.7.F Rheumatic and Other Valvular Heart Diseases--Health Services and Mental Health Administration

RMPS, HSMHA, has supported 23 programs in pediatric cardiology in 16 regions. Five of these programs have been limited to rheumatic fever or streptococcal cultures. The others have dealt with all types of pediatric cardiac disease. Although RMPS funding for some of these has been terminated, most have become self-supporting or were continued under other funding sponsorship. These projects (for which no further descriptions were available) and their level of support in FY 72 were:

- Prevention, Diagnosis and Treatment (FY 72: 12 programs, $455,838)
- Screening (FY 72: eight programs, $153,666)
- Training and Education (FY 72: three programs, $87,200).

1.7.G Rheumatic and Other Valvular Heart Diseases--National Aeronautics and Space Administration

For description of NASA supported activities related to rheumatic and other valvular heart diseases, see topic discussions in Section 1.2.G.

1.7.H Rheumatic and Other Valvular Heart Diseases--National Science Foundation

In FY 72 the National Science Foundation funded and administered one program (FY 72 funding: $20,000) to investigate blood flow in aortic valve models.

- Blood Flow Past Aortic Heart Valves. A numerical technique capable of solving unsteady axisymmetric viscous flows with moving boundaries is to be developed. The technique will be used to investigate the hydrodynamic characteristics of blood flow past aortic valve models. The effects of the leaflet motion on the pulsatile flow processes will be investigated. Hydrodynamic characteristics for models of the healthy aortic valves will be compared with those for stenotic ones. The numerical method to be developed can be applied to other biological flow problems with moving boundaries.

1.7.I Rheumatic and Other Valvular Heart Diseases--Social and Rehabilitation Service

A number of projects funded and administered by the SRS are applicable in some measure to this area. They are concerned with the development of techniques and criteria for exercise testing, work tolerance and rehabilitation. These projects are listed under Section 1.2.I

(Coronary Heart Disease). The SRS provides third party payments for provision of care (which may involve participation in clinical research).

1.7.J Rheumatic and Other Valvular Heart Diseases--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

1.7.K Rheumatic and Other Valvular Heart Diseases--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

1.7.L Rheumatic and Other Valvular Heart Diseases--Veterans Administration

For a discussion of VA projects relevant to this area, see Sections 1.2.L and 1.6.L.

1.8 CARDIOMYOPATHY

1.8.A Cardiomyopathy--Department of Agriculture

No identified USDA supported research is directly related to this area.

1.8.B Cardiomyopathy--Atomic Energy Commission (AEC)

The AEC funds and administers contract-supported studies in this area (FY 72: one onsite contract, totalling $111,000).

- Investigators at the Franklin McLean Memorial Research Institute are studying biochemical correlates of experimental cardiac hypertrophy in rats. In this research, molecular alterations associated hypertrophy of muscle fibers and hyperplasia of connective tissue cells are investigated in animals with surgically induced constrictions in the ascending aorta. Among the cellular parameters of interest are:

  - Synthesis, degradation, and turnover of cardiac myosin
  - Collagen synthesis
  - DNA synthesis in the interstitial (connective) tissues.

AEC supported research on nuclear medicine technology, which is discussed in Section 1.2.B (Coronary Heart Disease) is also pertinent to cardiomyopathy.

1.8.C Cardiomyopathy--Department of Defense

No identified ongoing DOD supported activities are directly related to this area.

NHLI

1.8.D Cardiomyopathy--Environmental Protection Agency

The Community Health and Environmental Surveillance Studies of the Human Studies Laboratory of EPA (See Section 2.2.D for description of CHESS) includes analyses of the effects of atmospheric pollution on persons with chronic heart diseases.

1.8.E Cardiomyopathy--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

1 8.F Cardiomyopathy--Health Services and Mental Health Administration

The National Institute on Alcohol Abuse and Alcoholism (NIAAA), HSMHA, funds and administers research related to this area.

Among the NIAA supported projects are:

- Alcoholism and Diseases of the Heart (FY 72: one grant, totalling $57,333). This is a study of the response of the heart to chronic ethanol ingestion, physiological and biochemical definition of the lesion produced, and approaches to its modifications or reversibility. Left ventricular disease is to be studied among three groups of patients who are habitual users of ethanol:
  - Noncardiac alcoholics who have normal cardiac size, EKG, and no cardiac symptomatology,
  - Inpatient alcoholic subjects under 45 years of age who are ambulatory, without clinical evidence of heart disease, and are not agreeable to a rehabilitation program, and

- Patients under 45 years of age with a single or repeated episode of left ventricular heart failure. Sex of the subjects is not specified. In addition, a number of metabolic studies will be done on dogs that have been induced to ingest large quantities of ethanol.

- The Effect of Alcohol on the Heart (FY 72: one grant, totalling $38,700). The objective of this study is to determine the sequence of events leading to the production of severe myocardial disease in alcoholics. Ethanol is being given chronically to infant chimpanzees, rhesus monkeys and dogs as drinking fluid or as part of a liquid diet. Day-to-day changes in myocardial function are studied through the use of radioactive rubidium and ultrasound echo recording. Numerous other studies of myocardial metabolism will be done.

The RMPS, HSMHA, has supported production of one guideline document on cardiomyopathy entitled "Recognition and Prevention of Cardiomyopathy." This is currently undergoing revision and will be published with the other Intersociety Commission of Heart Diseases (ICHD) documents in book form by the end of the summer. (FY 72 funding is presented in Section 1.1.F.)

1.8.G Cardiomyopathy--National Aeronautics and Space Administration

For description of NASA supported effort related to cardiomyopathy, see Section 1.2.G.

1.8.H Cardiomyopathy--National Science Foundation

The NSF funds and administers one project related to this area.

- Myofibrillar Assembly in Cardiac Muscle. See Section 1.2.H for project description.

1.8.I Cardiomyopathy--Social and Rehabilitation Service

No identified ongoing SRS supported research activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

1.8.J Cardiomyopathy--Social Security Administration

No identified ongoing SSA supported research activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

1.8.K Cardiomyopathy--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

1.8.L Cardiomyopathy--Veterans Administration

The VA funds, conducts and/or administers studies related to cardiomyopathy. (No information on FY 72 funding was available for this report.) The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics. These studies include:

- Studies of the Effect of Ethyl Alcohol on the Heart. Surmising that the depressant effects of ethyl alcohol on the heart can be obscured by alcohol's known release of the stimulating hormone epinephrine, studies were combined with the blockade of this stimulation in dogs. Alcohol and blockade produced progressive deterioration of cardiac function. Alcohol without blockade caused both stimulation and

depression in different animals for 30 minutes followed by progressive depression that was less severe than in the blockade group. The hypothesis noted offers an explanation for the stimulating effect seen in normal subjects, the unresponsiveness reported in subjects with unrecognized heart diesease and the depressant changes observed in patients with known heart disease.

The effect of alcohol on the heart's metabolism was studied in anesthetized dogs by serial sampling of small muscle specimens from the heart using a biopsy catheter. Fifteen minutes after starting infusions of alcohol that produce moderate intoxication, biochemically detectable increments of neutral fat begin to accumulate in the heart. The faster the infusion rate of alcohol, the faster the accumulation of fat. The deposition of fat was accompanied by progressive deterioration of cardiac performance. These findings illustrate that the toxic effects of alcohol are immediate and disturb simultaneously metabolic and hemodynamic functions.

For additional VA studies relevant to this area, see Section 1.2.L.

1.9 ARRHYTHMIA

1.9.A Arrhythmia--Department of Agriculture

No identified ongoing USDA supported research is directly related to this area.

1.9.B Arrhythmia--Atomic Energy Commission

The AEC funds and administers contract supported studies in arrhythmia (FY 72: one onsite contract, $100,000; two offsite contracts, totalling $900,000).

An implantable, nuclear-powered cardiac pacemaker is being developed by the AEC's Division of Reactor Development and Technology. A prototype device has been developed and successfully tested for ruggedness and durability. This device is now being tested in dogs at NHLI. Some 30 dogs have been implanted thus far. Licensing of the pacemaker is now under discussion with the AEC Regulatory Office. It is anticipated that testing in human subjects will begin very soon. NHLI will also participate in the clinical testing program. (Note: All work performed on the cardiac pacemaker at NHLI is done at no expense to the AEC).

1.9.C Arrhythmia--Department of Defense

In FY 1972 the Department of the Army conducted one study entitled "Combined Standby Transvenous Defibrillator and Demand Pacemaker for Army Patient Field Support." (This study was funded for $65,000.)

This work is designed to improve medical treatment of combat casualties by providing instrumentation for use in transvenous defibrillation of significant cardiac rhythm disturbances in high risk patients vulnerable to sudden onsets of fatal arrhythmias. The equipment will use pattern recognition of precursor electrocardiograph signals, such as ventricular tachycardia leading to ventricular fibrillation to institute therapeutic defibrillation prior to the onset of cardiac arrest. Two devices to be developed: an external one for use in an intermediate coronary care unit (ICCU) for patients who demonstrated significant cardiac rhythm disturbances while in an intensive care unit (ICU); and an implantable one for patients who consistently demonstrate serious rhythm disturbances.

In FY 72 the Department of the Air Force funded three studies in cardiovascular disease (no project descriptions or level of funding data were available at time of preparation of this report) on (1) aortic insufficiency, (2) right bundle branch block and (3) left bundle branch block.

1.9.D Arrhythmia--Environmental Protection Agency

No identified ongoing EPA supported research relates directly to this area.

1.9.E Arrhythmia--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

NHLI

1.9.F Arrhythmia--Health Services and Mental Health Administration

The NIMH, HSMHA, funds and administers research in the area of arrhythmias.

Among the NIMH supported research is:

- A Study of Psychologic and Neural Factors in Cardiac Arrhythmias (FY 72: one grant, totalling $91,870). Although psychological factors are known to affect the development of and recovery from heart disorders, the precise relation between the activity of the nervous system and cardiac malfunction is not clear. This investigation plans to uncover some of the psychological and physiological correlates of coronary disease, and will explore the use of operant conditioning for the control of arrhythmia. Human heart patients and dogs are under study.

The RMPS, HSMHA, funded and administered general Emergency Medical Service (EMS) capabilities programs to improve EMS, to improve equipment for ambulances and to improve the training of EMS personnel to handle cardiac emergencies. (FY 72: 28 programs, $8,360,000).

In addition, the HSMHA supports, with RMPS funds, demonstration of the above capabilities. (FY 72: five programs, $8,000,000.)

1.9.G Arrhythmia--National Aeronautics and Space Administration

For description of NASA supported activities relevant to arrhythmia, see topic discussion in Section 1.2.G.

1.9.H Arrhythmia--National Science Foundation

For a description of NSF supported activity in this area, see Section 1.2.H (Coronary Heart Disease).

1.9.I Arrhythmia--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitation activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

1.9.J Arrhythmia--Social Security Administration

No identified ongoing SSA supported research activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

1.9.K Arrhythmia--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

1.9.L Arrhythmia--Veterans Administration

The VA funds, conducts and/or administers a number of studies related to arrhythmia. (No information on FY 72 funding was available for this report.) The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics. These studies include:

- Mechanism of Intraventricular Conduction and Excitation of the Endocardium. An extensive investigation has been made into the mechanisms by which the cardiac impulse is conducted through the intraventricular conducting system and transmitted from the conducting system into ordinary ventricular muscle. Such a study is relevant clinically because of the recent evolution of the concepts of block within portions of the specialization conduction system. These concepts require an hypothesis that block may occur within localized regions of the conducting system and cause conduction delay to corresponding regions of ventricular muscle. The data have shown to date that such an hypothesis may not be tenable because of profuse interconnections within the specialized conducting tissue which can bypass regions of localized block. On the basis of the data that have evolved to date it appears that such patterns of block (referred to clinically as "hemiblock") may require large areas of distal conducting system disease rather than small proximal lesions which are located at a critical area.

- Endocardial Activation of the Conducting System of the Canine and Primate Myocardium. The study has shown to date that there is a continuous ring of specialized conducting system and has also shown that the major input into the myocardium occurs in the lower third of the septum and is not necessarily associated with specific specialized conducting system. Studies have also begun on human atrial and ventricular myocardium removed at the time of open heart surgery and the effects of various drugs on these preparations have been studied. It has been shown that the effects of catecholamines and acetylcholine have both positive inotropic and restorative powers as far as the electrophysiologic properties are concerned of the depressed human myocardium. The third line of this research project is an attempt to determine a model for the study of supraventricular arrhythmias, specifically Wolff-Parkinson-White Syndrome and supraventricular tachycardia with block in the newborn puppy. Preliminary experiments have been carried out which so far reveal that this may be an ideal model for the future study for these specific arrhythmias.

- Effect of Drugs on Normal and Abnormal Conduction System. Studies of atrioventricular conduction in patients with short PR intervals and normal QRS complexes have revealed to date that this type of accelerated conduction is common in the normal population. It has been found that larger doses of propranolol are necessary in order to produce the desired degree of atrial ventricular block in these patients. This finding is important in the treatment of the arrhythmias which are prone to occur in these patients.

- VA Study of Electrical Activity of the Heart. This study involves the investigation of electrical discharge and recharge which accompanies each stroke of the heart pump. These phenomena are being examined at four levels:

  - The use of computer models of the heart and the chest to explore the relationship between the electrical state of the various regions of the heart and the simultaneous voltage pattern that results on the chest surface,

  - Experiments designed to compare the effect of local changes in chemical or mechanical behavior of heart muscle with accompanying changes in electrical activity,

  - Development of a library of extensive total chest surface recordings of electrocardiographic potential in human subjects with and without heart disease, and

  - Exploration of the applicability of advanced electrocardiographic techniques to the understanding and management of clinical heart disease.

  Other studies within this investigation have included:

  - Further observations on the effect of the aerosols on the electrical conducting system of the heart and the conditions under which exposure may lead to sudden death,

- Critical statistical evaluation of ECG criteria for right heart enlargement in the adult with a recommendation for clinical application, and

- Pilot development of high-frequency electrocardiographic criteria for mass screening in the detection of heart disease.

For information on additional VA studies related to arrhythmia see Sections 1.2.L and 2.3.L.

1.10 CARDIAC FAILURE

1.10.A Cardiac Failure--Department of Agriculture

No identified ongoing research of the USDA relates directly to this area.

1.10.B Cardiac Failure--Atomic Energy Commission

The AEC funds and administers several research projects related to this area:

- Artificial Heart Studies (See Section 1.2.B, Coronary Heart Disease, for topic description)
- Adverse Effects of Radiation and Heat from the Power Source of an Artificial Heart (See Section 1.2.B, Coronary Heart Disease, for topic description).

For description of additional related research activities supported by AEC, see Section 1.2.B (Coronary Heart Disease) dealing with the artificial heart and Section 4.6.B (Transplantation).

1.10.C Cardiac Failure--Department of Defense

No identified ongoing DOD supported research relates directly to this area.

1.10.D Cardiac Failure--Environmental Protection Agency

No identified ongoing EPA supported efforts relate directly to this area.

NHLI

1.10.E Cardiac Failure--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

1.10.F Cardiac Failure--Health Services and Mental Health Administration

The NIAAA, HSMHA, funds and administers research related to the area of cardiac failure.

Among the NIAAA supported projects are:

- Alcoholism and Diseases of the Heart. (See Section 1.8.F, on Cardiomyopathy for description of project.)
- The Effect of Alcohol on the Heart. (See Section 1.8.F, on Cardiomyopathy for description of project.)

1.10.G Cardiac Failure--National Aeronautics and Space Administration

The Biomedical Research Division, NASA, funds and administers research related to this area.

- Effects of Space Flights on Vascular Permeability (an in-house study, FY 72: $18,000). The objectives of this study are:
  - To locate and identify a permeability factor associated with blood vessels

- To see if this permeability factor protects and helps regulate the endothelial membrane lining the blood vessels

- To see if this same factor is associated with red blood cells

When the above is completed, autoimmune response studies will be initiated.

For additional related NASA projects, see Section 1.2.G.

1.10.H Cardiac Failure--National Science Foundation

For description of related research activities supported by NSF, see Section 1.2.H (Coronary Heart Disease).

1.10.I Cardiac Failure--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitation activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

1.10.J Cardiac Failure--Social Security Administration

No identified ongoing SSA supported research activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

1.10.K Cardiac Failure--Department of Transportation

No identified ongoing DOT supported research activities relate directly to this area.

1.10.L Cardiac Failure--Veterans Administration

The VA funds, conducts and/or administers a study related to cardiac failure (no information on FY 72 funding was available for this report). The project is being supported as part of the intramural research and patient care activities in VA hospitals and clinics.

- Experimental Congestive Heart Failure in Animals. This project is concerned with the relationship between cardiac concentration of digitalis and the serum concentration in the experimental animal (with an enlarged or atrophied heart).

For additional information on VA studies related to cardiac failure see Section 1.2.L.

1.11 SHOCK

1.11.A Shock--Department of Agriculture

No identified ongoing USDA supported activities relate directly to this area.

1.11.B Shock--Atomic Energy Commission

No identified ongoing AEC work is directly concerned with this area.

1.11.C Shock--Department of Defense

In FY 72, the Department of the Army funded and administered investigations related to cardiac shock (FY 72: nine contracts, totalling $476,000). These investigations include:

- A study designed to amplify normal protective mechanisms for deactivating circulatory peptides to reduce circulatory malfunctions
- A study designed to elucidate the ability of splenic and hepatic extracts in treating the endotoxemia in combat wound conditions such as peritonitis, burns, and hemorrhagic shock
- A study designed to characterize myocardial depressant factor (MDF) biochemically and physiologically and to determine the importance of MDF in relation to survival and/or alteration of critical physiologic events in situations of shock
- An investigation of the contractile state of the heart during hypovolemic shock to define the relationship between perfusion and ischemia and investigate drug effects on this relationship

NHLI

- A study designed to determine endocrine and pulmonary function directly preceding and succeeding the hemorrhagic shock associated with combat wounds, to discover a relationship among the hemodynamic, oxygen transport, and acid base variables in critically wounded suffering from any phase of shock to improve techniques of diagnosis and hence treatment

- A study designed to develop means of early identification of patients in hypovolemic shock states who do not respond to conventional therapy and to develop successful therapy for surgery to treat these refractory shock states

- A study designed to determine microcirculatory response to trauma.

1.11.D Shock--Environmental Protection Agency

No identified ongoing activities of the EPA relate directly to this area.

1.11.E Shock--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment.

1.11.F Shock--Health Services and Mental Health Administration

No identified ongoing HSMHA supported activities are related directly to this area.

1.11.G Shock--National Aeronautics and Space Administration

No identified ongoing NASA supported activities are related directly to this area.

1.11.H Shock--National Science Foundation

No identified ongoing NSF supported activities are related directly to this area.

1.11.I Shock--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitation activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

1.11.J Shock--Social Security Administration

No identified ongoing SSA supported research activities relate to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

1.11.K Shock--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

1.11.L Shock--Veterans Administration

The VA funds, conducts and/or administers a number of studies related to shock. (No information on FY 72 funding was available for this report). The projects are being supported as part of the intramural research and patient care activities in VA hospitals and clinics. These studies include:

- Mechanisms of Hemorrhagic Shock and Emergency Treatment. During FY 72, this study was involved in the investigation of the mechanisms of hemorrhagic (blood loss) shock, and an assessment of various intravenous fluids for emergency treatment. Baboons served as an experimental model for these studies because they most closely resemble man in the response to shock. This research aims at providing a rationale for safer emergency treatment of shock. To date, this work has indicated that the more easily transported and considerably cheaper physiologic salt solutions are at least as good and safe, if not better and safer, than the more expensive plasma-like intravenous fluids. These findings have implications also for cost reduction in the care of severely injured patients.

- Bio-Instrumentation--Cardiogenic Shock. Among these VA sponsored investigations is a study of a new assisted circulation technique which uses a pulsatile pump and disposable blood oxygenator to support the circulation in patients with cardiogenic shock. This "artificial heart" temporarily supports the pumping action of the heart from outside the body, and hopefully can be used in patients for several days. Preliminary studies in dogs have shown that the system is easy to use and not traumatic to blood components or other physiologic variables of the animals. It is anticipated that the system will be used in patients during the coming year.

II. LUNG DISEASES

II. LUNG DISEASES

Sections 2.1 through 2.14 outline activities supported in FY 72 by 11* of 12 Federal agencies correlated with the 14 major problem areas identified by the Lung Diseases Panel and its supporting task groups. The fourteen areas discussed are:

- The Normal Lung (2.1)
- Environmental Respiratory Diseases (2.2)
- Emphysema and Chronic Bronchitis (2.3)
- Pediatric Obstructive Respiratory Diseases (2.4)
- Allergic Airway Diseases - Asthma (2.5)
- Diffuse Interstitial Respiratory Diseases (2.6)

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*EPA is the exception. FY 73 data are presented since it is EPA's first full year of operation.

NHLI

- Infectious Respiratory Diseases (2.7)
- Sarcoid and Granulomatous Lung Diseases (2.8)
- Hypersensitivity Lung Diseases (2.9)
- Pulmonary Vascular Disease (2.10)
- Hyaline Membrane Disease of the Newborn (2.11)
- Cystic Fibrosis (2.12)
- Acute and Chronic Respiratory Failure (2.13)
- Extrapulmonary Manifestations of Respiratory Diseases (2.14).

2.1 THE NORMAL LUNG

2.1.A The Normal Lung--Department of Agriculture

No identified ongoing USDA supported research activities are related directly to this area.

2.1.B The Normal Lung--Atomic Energy Commission

The AEC funds and administers contract-supported studies on the normal lung (FY 72: three onsite contracts, totalling $695,000).

- At the Lovelace Foundation (Fission Product Inhalation Laboratory), Pacific Northwest Laboratory, and University of Rochester, extensive research is in progress on the physiology of the normal lung, including investigations of mechanisms (mucociliary action and macrophage activity) by which particulate matter is cleared from the lungs. These studies include research on the relationship of the anatomical structure of the lower respiratory tract to the deposition and retention of particulates of various types, as well as investigations into the role of pulmonary macrophages in the clearance of respirable particles. As a part of the physiological studies, research is also conducted on the development of physical (morphologic) and conceptual (mathematical) models of the lung. Another study (Pacific Northwest Laboratory) seeks information on certain aspects of the morphology of the human lung (determination of epithelial thickness in the conductive airways and characterization of tracheobronchial lymph nodes). At the molecular level, comparative studies of pulmonary lipids (particularly surfactants) in four mammalian species (dog, horse, sheep, and hamster) are in progress (Lovelace Foundation). The biosynthesis of lipids (primarily surfactants) in lung tissue of the rat and hamster is under investigation in a related study (Pacific Northwest Laboratory).

NHLI

- Research on lung modeling by AEC (onsite) contractors at the Lovelace Foundation is also supported by a National Institute of Environmental Health Sciences (NIEHS) contract (FY 72: one contract, $100,000).

2.1.C The Normal Lung--Department of Defense

The Department of the Army funded and administered eight programs directed primarily at investigations of the reaction of the normal lung to abnormal or stressful situations (FY 72: eight programs, totalling $223,000). Included among the objectives of these programs are:

- Examination of several factors that contribute to or result from defective tissue oxygenation and blood supply following injury and shock such as pulmonary insufficiency and oxygen toxicity, alterations in the oxygen transport characteristics of stored blood, the microaggregate of leukocytes and platelets that develop in stored blood and *in vivo* following shock and trauma, and the alteration in energy metabolism of the gastric mucosa

- Studies of the influence of hypoxia on the pulmonary microcirculation to determine the site and mode of operation vasopressor response to inspired mixtures of low oxygen

- A demonstration that a period of impaired hypothalamic oxidated mechanism results in autonomic dysfunction which may cause pulmonary vascular changes

- Investigation of the relationship between chemoreceptor sensitivity to hypoxia and the degree of adaptation to high elevation by isocapnic hypoxia sensitivity tests under steady state conditions at rest

- Definition of natural history of lung function in burned patients to elucidate the pathogenesis of pulmonary complications the early post burn state

- Development of an objective test (133 xenon lung scan) for the early diagnosis of inhalation injury in combat wounded personnel; and

- A study to determine if increased ventilation (in respiratory minute volumes--to 70 L/min--and in tidal volumes--up to 30 ml/kg body weight) is harmful.

2.1.D The Normal Lung--Environmental Protection Agency

The Clinical Laboratory Programs of the EPA Human Studies Laboratory consist of analysis of the effects of atmospheric pollution on human health. Three categories of activities are funded: in-house studies, extramural contract supported studies and extramural grant supported studies.

The in-house studies (FY 73: $425,000) include:

- Effects of air pollution on pulmonary defense mechanisms
- Effects of air pollution on normal growth of lung function in children
- Effects of carbon monoxide on coronary artery disease and the outcome of myocardial infarction
- Pollutant induced changes in patients with cardiovascular disease.

The contract supported studies (FY 73: $492,000) include:

- Development of techniques for studying human pulmonary defense mechanisms
- Effects of air pollution on the growth of lung functions
- Interaction of various pollutants on the causation of pulmonary disease
- Pulmonary effects of chronic exposure to oxidants

- Carbon monoxide effects on myocardial infarctions in humans and in monkeys
- Effects of carbon monoxide on persons with coronary artery disease.

The grant supported studies (FY 73: $217,000) include:

- Effects of atmospheric pollution on human lung function
- Effects of pollution on lung development
- Physiologic response to atmospheric pollution
- Response of patients with chronic lung disease to pollution-free air
- Air pollution effects on airborne respiratory infections.

2.1.E The Normal Lung--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

2.1.F The Normal Lung--Health Services and Mental Health Administration

No identified ongoing HSMHA supported research activities are related directly to this area.

2.1.G The Normal Lung--National Aeronautics and Space Administration

The Biomedical Research Division, NASA, funds and administers both contract-supported and in-house studies in this area. This program of studies is designated primarily to determine the magnitude of certain changes of pulmonary function under conditions of weightlessness--and to determine their effects on the ability of man to adjust successfully to spaceflights of long duration and to readjust to normal gravity subsequent to such a mission. In addition, the part played by gravity in determining pulmonary function on earth is being examined to obtain baseline data and improve the predictions which can be made regarding the changes expected in weightlessness.

- A Study of the Effects of Weightlessness and Gravity on Pulmonary Function (FY 72: one contract, $75,000). The objectives of this study:

  - To determine the effects of gravity in producing mechanical deformation of the lung and subsequent alterations in pulmonary function, and

  - To continue ground-based work on a pulmonary function experiment package which may be suitable at a later date for a flight experiment.

  The study also involves the development of a mechanical model of the human lung which will predict deformation under varying intensities and directions and the resultant effects on pulmonary function. Those portions of the lung affected by airway closure with variations in accelerations are examined.

- Pulmonary Function Test System (FY 72: one contract, totalling $50,000). The objective of this study is to evaluate, with human subjects, a laboratory system designated to provide a comprehensive evaluation of the pulmonary function in man.

NHLI

- Effects of Gravity on Aerosol Deposition and Pulmonary Defense Mechanisms (FY 72: in-house project, $25,000). The objective of this study is to determine the changes produced in the deposition of aerosols in the lungs by alterations in gravity.

- Basic Studies in Respiratory/Metabolic Physiology (FY 72: one contract, totalling $50,000). The objectives of this study are:

  - To explore the physiological mechanisms involved with the significant reduction of aerobic capability demonstrated during exercise while breathing increased levels of inspired pCO_2

  - To develop and evaluate potential pulmonary function measurements and procedures for application to spaceflight

  - To investigate the effect of the addition of 6 mm Hg CO_2 into the inspired gas during the measurement of metabolic rate

  - To investigate and recommend exercise protocols for obtaining heart rate vs. metabolic rate calibration curves.

- Mathematical Model of Metabolic/Respiratory Function (the simulation and integration of physiological regulatory mechanisms) (FY 72: one contract, totalling $50,000). The objectives of this study are:

  - Identify all available previous and present research relating to physiological algorithms

  - Identify those subsystems which are not advanced sufficiently for inclusion in a total body algorithm and provide for their future development

  - Integrate and verify on a subsystem level until all major homeostatic systems are represented

  - Develop an interactive computer system which will permit use of the simulation system by any interested research personnel.

This approach--of mathematical simulation--should permit the identification of the gaps in present knowledge and also permit a basis upon which to place new fundings.

- Physiological Verification of Mixed Gas Atmospheres (FY 72: one contract, totalling $100,000). This study continues the prior investigation of the decompression hazards associated with the utilization of mixed gas atmospheres. It is designed to investigate alternate methods of denitrogenation which would provide the necessary decompression protection without impacting the prelaunch schedule and to conduct studies in an attempt to obtain objective information regarding decompression sickness symptoms.

NASA, in FY 72, funded and administered two programs (funded at $70,000) related to pulmonary diagnostics. The studies were:

- Minature Respiration Measurement System. The accurate determination of instantaneous respiratory flow over the dynamic range required during exercise is a demanding problem. This problem is further complicated when requirements of small weight and volume as well as changing atmospheric pressure and composition are imposed. There are no commercial flowmeters which meet these requirements. A prototype bidirectional turbine flowmeter has been developed which has high resolution and unidirectional accuracy. The objective of this effort is to advance the state of the art in respiratory flowmeters. Although the turbine flowmeter suffers from inertial and dynamic problems, initial work in this area has shown the feasibility of decreasing the turbine weight by utilizing advanced manufacturing methods. Also an electronic corrector circuit can be designed to eliminate any remaining dynamic error. This development work concentrates on these two areas.

NHLI

- Development of a Respiratory Quadrupole Mass Spectrometer. The measurement of respiratory gas exchange while working in a pressure suit continues to be a difficult problem. NASA has been continuously asked to determine or estimate metabolic expenditure during life support qualification tests in which this measurement is of primary importance for acceptance of the equipment. This device would also have wide application in a wide spectrum of measuring respiratory phenomena. A design for a prototype small quadruple mass spectrometer has been completed and hardware fabrication is underway.

2.1.H The Normal Lung--National Science Foundation

In FY 72, the NSF funded and administered five programs (FY 72 funding: $212,000) directed at a basic understanding of the dynamic relationships within the pulmonary and cardiovascular systems.

- Fluid Mechanics Problems Related to Biological Flow Phenomena. The primary aim of this investigation is to identify and study several fluid mechanics problems which are directly related to biological flows using viable mathematical models as well as simplified laboratory models whenever the latter is feasible and desirable. Four basic areas of investigation are: peristaltic pumping, mucociliary pumping, blood flow rheology in large vessels, and precorneal liquid film on the human eye.

- Interfacial Fluid Dynamics. The object of this investigation is the study of fluid dynamics problems that involve fluid-fluid and fluid-solid interfaces. In particular the following problems are being examined:

  - The interaction of interfacial tension forces and membrane elasticity in the alveoli relating to the "elasticity" of human and animal lungs

  - Heat and mass transfer across fluid-fluid interfaces.

- Oscillatory Fluid Flow in Lungs. A theoretical and experimental study of the relationship between pressure and flow, in phase and amplitude, in a system of branching tubes is being carried with the incoming flow being oscillatory. The geometry of the system and the fluid dynamical parameters are chosen to represent the larynx, the trachea, and the first two generations of bronchi. Results will be compared with *in vivo* measurements.

- Stochastic Modeling and Analysis of Lung Tissue Elasticity. A stochastic approach to the quantitative study of the mechanical behavior of the lung is planned. The mathematical modeling and analysis of alveolar walls will be first examined, followed by a consideration of the structural strength of the basic respiratory unit consisting of an alveolar duct and its associated alveoli. Based on these studies, attempts will be made to establish mathematical models which predict behavior of tissue slabs in saline, the pressure volume saline behavior of the lung, and, finally, an attempt will be made to predict the response behavior of the air-filled lung. Existing and new experimental data will be carefully correlated with the analytical results.

  Three basic analytical approaches are planned. The first is based upon the theory of composite materials, the second is a stochastic differential equation approach, and the third is based upon random walk models.

- Cardiopulmonary Dynamics (See Section 1.2.H for description of project.)

2.1.I The Normal Lung--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitative activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

2.1.J The Normal Lung--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.1.K The Normal Lung--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.1.L The Normal Lung--Veterans Administration

The VA conducts research related to this area. (No information on FY 72 funding was available for this report.) The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics.

Among studies related to the normal lung conducted by the VA is the following:

- Biologically Active Polypeptides From the Lung. The lung is active in the metabolism of vasoactive hormones but, with the possible exception of bradykinin, no vasoactive polypeptides have been extracted from normal lung. In this study, several peptide fractions possessing biological activity on vascular and nonvascular smooth muscle have been prepared. These vasoactive lung polypeptides (VLP) are the first such peptides to be extracted from the lung. In addition to their systemic and pulmonary vasodilator actions, they relax the bronchi and either relax or contract the stomach. Since the peptides are still in an impure state, investigation of their biological actions and possible importance in health and disease must await their availability in pure or nearly pure form.

NHLI

2.2 ENVIRONMENTAL RESPIRATORY DISEASES

2.2.A Environmental Respiratory Diseases--Department of Agriculture

The USDA funds and administers or conducts research related to this area (FY 72: six projects, no funding data available).

The projects conducted are:

- Tobacco Smoke Constituents and Ultrastructural Cell Changes in Tracheal Tissue. The objective of this study is to develop a new bioassay method based on ultrastructural cell changes in tracheal tissue of rodents brought about by tobacco smoke constituents.
- Effect of Cigarette Smoke on the Respiratory Epithelial Cell Turnover Rates in Mice. The objective of this study is to develop a new bioassay method based on respiratory epithelial cell turnover rates in mice.
- Effect of Tobacco Smoke on Lipid Uptake in Animal Tissue. The objective of this study is to develop a new bioassay method based on the effect of tobacco smoke on lipid uptake in animal tissue.
- Effect of Tobacco Smoke Components on Chromosomal Aberrations of Rodents. The objective of this study is to develop a rapid bioassay procedure based upon the effects of tobacco smoke constituents on chromosomes, tissues, and organs following oral and intravenous administration.

2.2.B Environmental Respiratory Diseases--Atomic Energy Commission

The AEC funds and administers studies in the area of environmental respiratory diseases (FY 72: four onsite contracts, totalling $3,745,000; two offsite contracts, totalling $54,000).

NHLI

- A broad program of research on the toxicity of inhaled environmental toxicants, particularly radioactive materials, is conducted at the Lovelace Foundation, Pacific Northwest Laboratory, and University of Rochester. In these studies, beagle dogs and rodents are exposed to graded doses of radioactive aerosols in order to define and quantitate long-term effects of radiation in the lungs and other organ systems (including spatial and temporal aspects of the radiation response). The metabolism of soluble and insoluble radioactive aerosols is investigated to elucidate the relative sensitivity of lung, lymph nodes, liver, and bone to protracted but changing dose rates. Data from long-term studies of these sorts are required for the formulation of meaningful radiation protection guides. These data also serve as a basis for the evaluation of biological consequences associated with occupational and population exposures to man-made radiation. At the present time, low doses of alpha-emitting radionuclides are of particular interest. Mechanisms of pulmonary injury as well as the early detection of pathologic changes in the lungs are investigated as part of the overall effort. Therapeutic measures (lung lavage, chelate therapy, and stimulation of phagocytic activity) designed to reduce body burdens of radionuclides are also being developed. It is worthy of note that research at the Pacific Northwest Laboratory includes the study of combined effects produced by the inhalation of radioactive aerosols and chemical toxicants (cigarette smoke, carnotite ore, benzpyrene, chrysotile asbestos, and diesel fuel). Research conducted at two AEC (onsite) facilities on the uranium miner problem, which is a part of the inhalation radiotoxicology program, is facilitated by support from NIEHS (FY 72: one contract at the Pacific Northwest Laboratory, $350,000; one contract at the University of Rochester, $51,000).

- At the Los Alamos Scientific Laboratory, a different exposure technique is employed in the study of pulmonary effects produced by alpha radiation. Plutonium-containing microspheres are administered intravenously to Syrian hamsters in such a way that the particles lodge in the pulmonary microvasculature. The immobilized particles cause a protracted exposure of lung tissues to alpha radiation.

- Research at the University of Rochester is defining effects of several chemical toxicants (SO_2, NO_x, and amosite asbestos) on rates of clearance of respirable particles (TiO_2) from the rat lung. This work is supported by NIOSH (FY 72: one grant, $59,000).

- In several laboratories, exfoliative cytology of sputum and broncho-pulmonary washings are being investigated as a means of early detection of pulmonary pathology (especially neoplasia) in humans and animals. Investigators at the Lovelace Foundation, Pacific Northwest Laboratory, and the University of Rochester are developing special techniques for the preparation and characterization of aerosols. Both physical and chemical characteristics of aerosols, including the absorption of toxic substances by inert particles of respirable size, are being studied. As techniques are perfected, they are utilized in the biological programs.

- A group in the Analytical Chemistry Division of the Oak Ridge National Laboratory is currently conducting a detailed analysis of substances present in cigarette smoke. A variety of analytical techniques is being employed to identify and quantitate both organic and inorganic substances in tars, particulates, the gaseous phase, and condensate. In addition, the Oak Ridge investigators are developing a special type of smoking machine for use in exposing rodents (mice and hamsters) to cigarette smoke and techniques for monitoring smoke composition during animal exposures. This research is supported by NCI (FY 72: one contract, $640,000).

The AEC also funds and administers a contract-supported program of research in nuclear medicine technology (FY 72: three onsite contracts, $580,000; two offsite contracts, $69,000), which includes a number of studies on normal and abnormal pulmonary function with emphasis on the early diagnosis of lung lesions and changes in pulmonary perfusion and ventilation. Other research in nuclear medicine is directed toward the development of general technologies (detector systems, radio-pharmaceuticals, image processing, etc.)

NHLI

applicable to a number of specific diseases, including those of the lungs. These studies interface with a number of lung-disease categories, particularly environmental lung diseases, emphysema and chronic bronchitis, pediatric obstructive respiratory diseases, and acute and chronic respiratory failure.

2.2.C Environmental Respiratory Diseases--Department of Defense

No identified ongoing DOD supported research activities are related directly to this area.

2.2.D Environmental Respiratory Diseases--Environmental Protection Agency

The EPA conducts a Pesticide Epidemiology Program (See Section 1.2.D for program description) which includes investigations of interstitial fibrosis caused by pesticides.

The Human Studies Laboratory of the EPA conducts Community Health and Environmental Surveillance Studies (CHESS). These are cooperative studies with research institutions in the U.S. (FY 73: in-house, $1,380,000; contracts, $4,010,000).

The CHESS Program couples the measurement of human health indicators with measurement of atmospheric levels of pollution in 35 communities across the United States. The communities are selected to be as nearly alike as possible in all aspects except for air pollution. They are selected in three groups: high, intermediate, and low pollution. (Thus, the incidence,

NHLI

or prevalence, of the health indicators is determined across a gradiant of pollution). Health indicators include: (1) prevalence of chronic respiratory disease; (2) incidence of upper or lower respiratory disease; (3) pulmonary function in children; and (4) aggravation of symptoms in panels of susceptible individuals, including those with asthma, those with chronic lung disease, and those with chronic heart disease.

As a part of its Clinical Laboratory Programs (See Section 2.1.D for description), the Human Studies Laboratory of EPA conducts a program related to the interactions of various pollutants in the causation of pulmonary disease.

2.2.E Environmental Respiratory Diseases--Food and Drug Administration

No identified ongoing FDA supported research is directly related to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

2.2.F Environmental Respiratory Disease--Health Services and Mental Health Administration

The National Institute for Occupational Safety and Health (NIOSH) conducts studies of the incidence and prevalence of occupational respiratory diseases with particular emphasis on coal workers' pneumonoconiosis.

In addition, chest roentgenograms are being provided for all active coal miners in the United States under authority of the Federal Coal Mine Health and Safety Act of 1969.

NHLI

At NIOSH laboratories in Cincinnati studies are underway to determine the role of dusts and toxic chemicals contributing to respiratory diseases in workers.

(The total resources in this area were $3,285,000 for FY 72.)

2.2.G Environmental Respiratory Diseases--National Aeronautics and Space Administration

See Section 2.1.G for description of NASA research (particularly diagnostic techniques) relevant to this area.

2.2.H Environmental Respiratory Diseases--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

2.2.I Environmental Respiratory Diseases--Social and Rehabilitation Service

No identified ongoing SRS supported research is directly related to this area.

2.2.J Environmental Respiratory Diseases--Social Security Administration

The Federal Coal Mine Health and Safety Act of 1969 provides for the protection of the health and safety of persons working in the coal mining industry. Title IV of the Act provides monthly benefits to living coal miners who are totally disabled due to pneumoconiosis arising out of employment in coal mines and to surviving widows. The requirements for

entitlement and the amounts of the benefits are stated in the law.

[The Black Lung Benefits Act of 1972 (Public Law 92-303) made substantial changes to the original legislation.]

2.2.K Environmental Respiratory Diseases--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.2.L Environmental Respiratory Diseases--Veterans Administration

One study described in Section 2.3.L (Emphysema and Chronic Bronchitis) is applicable to this area, i.e., "Studies in Performance Bronchoscopy."

2.3 EMPHYSEMA AND CHRONIC BRONCHITIS

2.3.A Emphysema and Chronic Bronchitis--Department of Agriculture

The USDA funds and administers/or conducts research related to this area. (FY 72: one project, funding data not available.)

- A Study of Cardiopulmonary Physiology of Ruminants

  The objectives of this study are:

  - To establish an etiologic mechanism for acute bovine pulmonary emphysema
  - To study various aspects of ammonia toxicity
  - To establish an etiologic mechanism for brisket edema of cattle.

2.3.B Emphysema and Chronic Bronchitis--Atomic Energy Commission

See description of AEC program in Section 2.2.B, Environmental Lung Diseases.

2.3.C Emphysema and Chronic Bronchitis--Department of Defense

No identified ongoing DOD supported research activities are related directly to this area.

2.3.D Emphysema and Chronic Bronchitis--Environmental Protection Agency

As part of its Clinical Laboratory Programs (See Section 2.1.D for description), the Human Studies Laboratory of EPA funds and administers a contract to determine the

response of patients with chronic lung diseases to pollution-free air.

EPA's CHESS program (See Section 2.2.D for description) includes analysis of the effect of air pollution on incidence and severity of asthma and emphysema and chronic bronchitis.

2.3.E Emphysema and Chronic Bronchitis--Food and Drug Administration

No identified ongoing FDA supported research efforts are directly related to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

2.3.F Emphysema and Chronic Bronchitis--Health Services and Mental Health Administration

The Regional Medical Programs Service, HSMHA, has been supporting 21 adult respiratory disease programs aimed at the development of regional resources for demonstration of modern methods for the diagnosis and treatment of chronic respiratory disease and for the training of physicians, nurses and allied health personnel in the provision of excellent care for patients with these diseases. Total support provided in FY 72 was $1,627,000 for adult pulmonary disease programs.

2.3.G Emphysema and Chronic Bronchitis--National Aeronautics and Space Administration

See Section 2.1.G for discussion of NASA research (particularly diagnostic techniques) relevant to this area.

NHLI

2.3.H Emphysema and Chronic Bronchitis--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

2.3.I Emphysema and Chronic Bronchitis--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitative activities are related directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

2.3.J Emphysema and Chronic Bronchitis--Social Security Administration

No identified SSA supported activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.3.K Emphysema and Chronic Bronchitis--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.3.L Emphysema and Chronic Bronchitis--Veterans Administration

The VA funds, conducts and administers several studies related to emphysema and chronic bronchitis. The following paragraphs describe those studies for which information was available. (No information on FY 72 funding was available for this report.) The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics.

NHLI

- Development of Experimental Models of Pulmonary Emphysema. A model of centrilobular emphysema has been produced in rats very strongly resembling the human lesion by administering cadmium chloride aerosol in an exposure chamber. This represents a very important advance since it will permit detailed study of the early stages of a lesion in animals which looks very much like one form of emphysema in man. The precise nature of the initial injury will need to be identified and possible methods of preventing the development of this lesion in response to the administration of cadmium aerosol will be explored. This work has special significance since another VA conducted study has shown that cigarette smokers have significantly more cadmium in their body tissues than do nonsmokers and that patients with chronic bronchitis and emphysema have significantly more cadmium in their tissues than nonsmokers. Furthermore, they have shown that the quantity of cadmium in cigarettes can probably account for the increased burden of cadmium found in the tissues of smoking individuals. Electron microscope and histological studies of chronic exposure to cadmium are presently underway.

- The Effects of Inhalation Therapy and Long-Term Follow-Up on the Course of Chronic Obstructive Lung Disease. It appears--from this study--that inhalation therapy causes further objective improvement in the ability of most patients to move air even though they have already had an optimal regimen established that does not include such therapy. Whether this improvement is sustained will be evaluated as the protocol progresses. (Project design and/or objective--not available.) This would be also applicable to 2.10.L (Pulmonary Vascular Disease) and to 2.13.L (Acute Chronic Respiratory Failure).

- Evaluation of Arterial Blood-Gas Changes. This project involves the evaluation of arterial blood-gas changes throughout the day and during the night in patients with advanced obstructive lung disease. Initial investigation has shown little significant variation of arterial blood gases

NHLI

during the day but striking decreases in oxygen levels and increases in carbon dioxide levels during sleeping hours. The significance of these findings for the use of night time oxygen therapy in patients with severe obstructive lung disease is presently under exploration. An investigation is being done on the effects of these severe alterations of blood gases on brain function. The possible role of these blood gases changes on producing cardiac arrhythmias is also under study.

- Studies in Performance Bronchoscopy. Studies have been initiated in the performance bronchoscopy with the flexible fiberoptic bronchoscope. In contradistinction to bronchoscopy with the rigid tube, this procedure is performed on the ward rather than in the operating room. The instrument is passed through the patient's nose with the patient sitting up on a chair which is much more comfortable than the recumbent position with the head thrown severely backward, the position required for rigid tube bronchoscopy. Furthermore, the flexible bronchoscope makes available several additional orders of the branches of the bronchial tree to inspection and sampling. The flexible bronchoscope appears to be so far superior to the rigid tube bronchoscope that there may be little continuing indication for the use of rigid tube bronchoscopy in diagnostic work.

  This work also applies to Section 2.2.L (Environmental Respiratory Diseases).

- Intensive Pulmonary Rehabilitation. This project involves clinical research designed to be of direct benefit to chronically-ill patients with the express goals of improving functional capacity and extending the time between readmissions of patients with chronic obstructive lung disease. The program is a two-week course of intensive physical conditioning and training in breathing and airway hygiene. Patients are then followed for extended time and results compared with similar patients who did not undergo the therapy.

2.4 PEDIATRIC OBSTRUCTIVE RESPIRATORY DISEASES

2.4.A Pediatric Obstructive Respiratory Diseases--Department of Agriculture

No identified ongoing USDA supported research activities are related directly to this area.

2.4.B Pediatric Obstructive Respiratory Diseases--Atomic Energy Commission

See description of AEC research in nuclear medicine technology presented in Section 2.2.B, Environmental Lung Diseases.

2.4.C Pediatric Obstructive Respiratory Diseases--Department of Defense

No identified ongoing DOD supported research activities are related directly to this area.

2.4.D Pediatric Obstructive Respiratory Diseases--Environmental Protection Agency

No identified ongoing EPA supported research activities are related directly to this area.

2.4.E Pediatric Obstructive Respiratory Diseases--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

2.4.F Pediatric Obstructive Respiratory Diseases--Health Services and Mental Health Administration

The Regional Medical Programs Service, HSMHA, has supported 12 regional pediatric pulmonary disease programs through grants and contracts and the Maternal and Child Health Administration has supported one under a contract. Each grantee or contractor has provided a regional resource for demonstration of modern methods of diagnosis and treatment of children with chronic respiratory disease and for the training of physicians, nurses and allied health personnel in the provision of care for these diseases. Each program has also provided consultation services for doctors and nurses in smaller and rural hospitals and clinics and has arranged teaching visits to such settings. Total support provided for these programs in FY 72 was $1,700,000 for RMPS and $150,000 for MCHS.

2.4.G Pediatric Obstructive Respiratory Diseases--National Aeronautics and Space Administration

No identified ongoing NASA supported research activities are related directly to this area.

2.4.H Pediatric Obstructive Respiratory Diseases--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

2.4.I Pediatric Obstructive Respiratory Diseases--Social and Rehabilitation Service

No identified SRS supported research and/or rehabilitative activities are related directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

2.4.J Pediatric Obstructive Respiratory Diseases--Social Security Administration

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.4.K Pediatric Obstructive Respiratory Diseases--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.4.L Pediatric Obstructive Respiratory Diseases--Veterans Administration

No identified ongoing VA supported research activities are related directly to this area.

2.5 ALLERGIC AIRWAY DISEASES--ASTHMA

2.5.A Allergic Airway Diseases--Asthma--Department of Agriculture

No identified ongoing USDA supported research activities are directly related to this area.

2.5.B Allergic Airway Diseases--Asthma--Atomic Energy Commission

No identified ongoing AEC supported research activities are related directly to this area.

2.5.C Allergic Airway Diseases--Asthma--Department of Defense

No identified ongoing DOD supported research activities are related directly to this area.

2.5.D Allergic Airway Diseases--Asthma--Environmental Protection Agency

The CHESS program (See Section 2.2.D for description) includes analysis of the effect of air pollution on incidence and severity of asthma and emphysema and chronic bronchitis.

2.5.E Allergic Airway Diseases--Asthma--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the

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development and testing of new drugs which may be used in research and treatment in this area.

2.5.F Allergic Airway Diseases--Asthma--Health Services and Mental Health Administration

The HSMHA funds and administers research related to this area.

Among these NIMH supported research projects is:

- A Study of Emotion and Pulmonary Function in Asthma (FY 72: one grant, totalling $93,501). This investigation involves the study of bronchial asthma, which the principal investigator believes is a psychoendocrine disorder in which certain emotional states lead to physiological disorders in the body. Patients with chronic perennial asthma and normal humans serve as the subjects of this study. While the subject converses, pulmonary function is measured for the study of the expressive meaning of respiratory movements. Airway resistance is measured by a whole body plethysmorgraph. A cardiotachometer is used to monitor heart rate as one index of the level of sympathetic activation and of sympathetic-parasympathetic balance in the cardiovascular system. Various drugs which constrict the bronchi are administered to some subjects in test doses to explore the relationship of the asthmatics' varying airway hyperactivity with variations in their emotional backgrounds. Clinical data are obtained from behavioral observations, urine specimens, and hematologic and blood steroid studies. Extensive psychiatric interviews and evaluation are also conducted.

Additional related research supported by HSMHA is described in Sections 2.3.F and 2.4.F.

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2.5.G Allergic Airway Diseases--Asthma--National Aeronautics and Space Administration

No identified ongoing NASA supported research activities are related directly to this area.

2.5.H Allergic Airway Diseases--Asthma--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

2.5.I Allergic Airway Diseases--Asthma--Social and Rehabilitation Service

No identified SRS supported research and/or rehabilitative activities are related directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

2.5.J Allergic Airway Diseases--Asthma--Social Security Administration

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.5.K Allergic Airway Diseases--Asthma--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.5.L Allergic Airway Diseases--Asthma--Veterans Administration

No identified ongoing VA supported research activities are related directly to this area.

2.6 DIFFUSE INTERSTITIAL RESPIRATORY DISEASES

2.6.A Diffuse Interstitial Respiratory Diseases--Department of Agriculture

No identified ongoing USDA supported research activities are related directly to this area.

2.6.B Diffuse Interstitial Respiratory Diseases--Atomic Energy Commission

No identified ongoing AEC supported research activities are related directly to this area.

2.6.C Diffuse Interstitial Respiratory Diseases--Department of Defense

No identified ongoing DOD supported research activities are related directly to this area.

2.6.D Diffuse Interstitial Respiratory Diseases--Environmental Protection Agency

No identified ongoing EPA supported research activities are related directly to this area.

2.6.E Diffuse Interstitial Respiratory Diseases--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

2.6.F Diffuse Interstitial Respiratory Diseases--Health Services and Mental Health Administration

No identified ongoing HSMHA supported research activities are related directly to this area.

2.6.G Diffuse Interstitial Respiratory Diseases--National Aeronautics and Space Administration

No identified ongoing NASA supported research activities are related directly to this area.

2.6.H Diffuse Interstitial Respiratory Diseases--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

2.6.I Diffuse Interstitial Respiratory Diseases--Social and Rehabilitation Service

No identified SRS supported research and/or rehabilitative activities are related directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

2.6.J Diffuse Interstitial Respiratory Diseases--Social Security Administration

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.6.K Diffuse Interstitial Respiratory Diseases--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.6.L Diffuse Interstitial Respiratory Diseases--Veterans Administration

No identified ongoing VA supported research activities are related directly to this area.

2.7 INFECTIOUS RESPIRATORY DISEASES

2.7.A Infectious Respiratory Diseases--Department of Agriculture

The USDA funds and administers research related to this area (FY 72: two projects, no funding data available):

- Influence of a Typical and Nonpathogenic Mycobacteria on the Reliability of the Tuberculin Test in Cattle. The objective of this study is to investigate the role and significance of a typical and saprophytic mycobacteria and related organisms on the occurrence of nonspecific sensitizations in cattle to the tuberculin test.

- Pleuropneumonia-Like Organism (PPLO) Infections in Poultry. The objective of this study is to investigate infections caused by PPLO, the strains of organisms involved, the modes of transmission, and the test of specific-pathogen-free (SPF) programs. Fundamental studies on PPLO will be undertaken using electron microscopy to determine the subcellular changes with infection.

2.7.B Infectious Respiratory Diseases--Atomic Energy Commission

The AEC funds and administers a contract-supported study in the area of infectious respiratory diseases (FY 72: one contract, totalling $150,000).

As part of the microbiological surveillance in the animal colony at the Oak Ridge National Laboratory Biology Division, mycoplasma respiratory infections are being characterized in several animal species. This effort has resulted in the development of improved techniques for detection. The Oak Ridge National Laboratory study includes similar work on parainfluenza virus infections.

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2.7.C Infectious Respiratory Diseases--Department of Defense

In FY 72, the Department of the Army funded and administered 11 projects ($665,000) related primarily to infectious respiratory diseases.

These projects focus on:

- Provision of a base for the development of chemotherapeutic agents and improvement of methods for the isolation and identification of drug resistant and sensitive strains of mycobacteria
- Evaluation and/or design of new methods which can be used for isolation, identification and drug susceptibility testing of pathogenic mycobacteria
- Determination of the immunological, chemical and physical characteristics of the adenovirus structural proteins
- Development of safe adenovirus vaccine
- Evaluation of the etiology and epidemiology of acute respiratory tract infections by specific examination of factors relative to pathogenesis of herpes virus hominis, and mycoplasma pneumoniae infections
- Sedation of the chemical nature of the cell membrane glycoprotein with which influenza viruses combine as the first step in the infective process and procedures which will interfere with this process with the ultimate objective of developing chemotherapeutic drug(s) against respiratory viruses
- Determination of the factors operative in host resistance to, and recovery from, viral infections--
  - Role of interferon, especially endogenous, preformed interferon,
  - Modification of host resistance by depletion of preformed interferon,

- Termination of cells of intact animal responsible for interferon production,

- Search for nonviral stimuli capable of increasing host resistance to virus infections.

- Recovery and identification of heretofore unrecognized respiratory viruses from throat washings, sputum, etc.

- Longitudinal surveillance of a population of young working adults

- Evaluation of vaccines and antiviral compounds using vaccine testing and volunteers and field trials

- Antibody responses to infectious organisms presented in aerosol particles of selected sizes by other parenteral roots employing influenza viruses as a model

- Development of improved subunits of influenza virus vaccines

- Development and characterization of attenuated antigenic variance of influenza viruses and ultimately in effect live vaccine and studies of the prevention, control and treatment of epidemic influenza.

In FY 72, the Department of the Air Force funded (at approximately $48,000) a project entitled "Acute Respiratory Disease Vaccine and Surveillance Program." The objectives of this study are: (1) to provide epidemiologic and detailed laboratory surveillance for the administration of live-attenuated adenovirus vaccines, types 4 and 7; (2) to predict epidemic Acute Respiratory Disease (ARD) patterns in advance or to identify an outbreak at early onset; (3) to provide real time information regarding ARD etiologic patterns at any given point in time.

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2.7.D Infectious Respiratory Diseases--Environmental Protection Agency

As a part of its Clinical Laboratory Programs, (See Section 2.1.D for description) the Human Studies Laboratory of EPA funds and administers a contract to determine the effects of air pollution on airborne respiratory infections.

2.7.E Infectious Respiratory Diseases--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

2.7.F Infectious Respiratory Diseases--Health Services and Mental Health Administration

The Division of Narcotics and Drug Abuse, NIMH, HSMHA funds and administers a study related to this area (FY 72: one grant, totalling $42,380).

This study is "The Effect of Marihuana Smoking On The Heart and Lungs."

The objective of this study is to: (1) determine the effects of marihuana smoking on intracardiac pressures, vascular resistances, cardiac output, left ventricular function, airway resistance, lung volumes, and diffusing capacity of the lungs, (2) establish the presence or absence of increased

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pulmonary infections in marihuana smokers, and (3) determine the effect of marihuana on alveolar macrophage function. The subjects are humans and dogs.

2.7.G Infectious Respiratory Diseases--National Aeronautics and Space Administration

No identified ongoing NASA supported research activities are related directly to this area.

2.7.H Infectious Respiratory Diseases--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

2.7.I Infectious Respiratory Diseases--Social and Rehabilitation Service

No identified SRS supported research and/or rehabilitative activities are related directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

2.7.J Infectious Respiratory Diseases--Social Security Administration

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.7.K Infectious Respiratory Diseases--Department of Transportation

No identified ongoing DOT supported research activities are directly related to this area.

2.7.L Infectious Respiratory Diseases--Veterans Administration

The VA funds, conducts and administers several studies related to Infectious Respiratory Diseases (no information on FY 72 funding was available for this report). The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics.

- Studies of the Biosynthetic Pathways and Control Mechanism of the Tubercle Bacillis. One of the problems under investigation is to determine how isoniazid (a drug used for the treatment of tuberculosis) kills the tubercle bacillus. It has been established that 0.5 ug/ml of isoniazid (close to the threshold level) immediately begins to inhibit the synthesis of mycolic acids in the mycobacterium tuberculosis and that this inhibition is complete after about 60 minutes. This event is closely followed by a loss of viability of the bacilli which reaches about 18 percent after 180 minutes. Thus the drug acts immediately on the synthesis of an important cellular component that is very specific to mycobacteria at a low concentration. These results strongly suggest that the inhibition in the synthesis of the mycolic acids may be the primary mechanism of action of isoniazid.

- Immunologic Response to Colonization and Infection of the Respiratory Tract. Patients who had tracheostomies performed for reasons other than pulmonary infection were observed for two weeks. Semiquantitative bacterial cultures and immunoglobulin determinations were performed serially on tracheal aspirates. Antibody titers against the bacterial species which eventually became dominant in each patient's tracheal secretions were also measured serially, both in serum and tracheal aspirates.

  Bacterial colonization of the trachea occurred rapidly in all patients. The bacteriologic and immunologic data from patients who developed pneumonia were compared with data from those who did not. Tracheal aspirates of the two groups showed no differences in immunoglobulin or antibody titer. Serum antibody titers increased serially in all

infected patients, but did not increase in all non-infected patients. The studies suggest that circulating antibody may be of greater importance than locally secreted antibody as a host defense against bacterial pneumonia in tracheostomized patients.

- Tuberculosis Cooperative Study Control Laboratory. Two studies are involved:

  - Rifampin Pilot Study #2. This study was designed to compare the effectiveness and tolerance of rifampin plus isoniazid and rifampin plus streptomycin with isoniazid-streptomycin in previously untreated patients with advanced, cavitary, bacteriologically proven pulmonary tuberculosis. Clinical and laboratory data from participating VA hospitals and laboratory data from the TB Control Laboratory were utilized for this study. Although the differences in bacteriologic response as measured by achievement of cultures free of tubercle bacilli at six months were not significant, advantages of the regimen consisting of rifampin plus isoniazid over streptomycin plus isoniazid and streptomycin plus rifampin were suggested, particularly when the emergence of drug-resistant tubercle bacilli during treatment was taken into account. The pilot study has lent support to the experience of others who have found rifampin to be a highly effective and well tolerated antituberculous drug.

  - Cooperative Study of Rifampin (#33). This study started in 1971. It is designed to give a controlled comparison of four single dose regimens using rifampin, isoniazid and ethambutol in treatment of pulmonary tuberculosis. Clinical and laboratory data from participating VA and Armed Forces Hospitals and laboratory data from the TB Control Laboratory are being utilized for this study. As of May 1972, four hundred and twenty-one (421) patients had been admitted to the study and patient intake will continue until the number is sufficient to permit final evaluation and conclusions.

2.8 SARCOID AND GRANULOMATOUS LUNG DISEASES

2.8.A Sarcoid and Granulomatous Lung Diseases--Department of Agriculture

The USDA funds and administers/or conducts research in this area (FY 72: two projects, no funding data available):

- Investigations of Tuberculosis of Cattle. The objectives of this study are: to develop better methods of isolation, propagation, characterization, and preservation; and to develop more specific antigens, allergens, and methods of diagnosis of tuberculosis.

- Investigation of Tuberculosis and Cellular Sensitivity. The objectives of this study are: to improve methods of isolation, cultivation, and identification of mycobacterium reevaluation of tuberculin test; to study certain serological methods, as hemiagglutination tests, fluorescent antibody technique, and modifications of the regular intradermal test for sensitivity to tuberculin; to search for agents responsible for stimulating sensitivity to tuberculin; and to determine whether cattle, reactive to tuberculin, will retain sensitivity to tuberculin.

2.8.B Sarcoid and Granulomatous Lung Diseases--Atomic Energy Commission

No identified ongoing AEC supported research activities are related directly to this area.

2.8.C Sarcoid and Granulomatous Lung Diseases--Department of Defense

No identified ongoing DOD supported research activities are related directly to this area.

2.8.D Sarcoid and Granulomatous Lung Diseases--
Environmental Protection Agency

No identified ongoing EPA supported research efforts are directly related to this area.

2.8.E Sarcoid and Granulomatous Lung Diseases--
Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

2.8.F Sarcoid and Granulomatous Lung Diseases--
Health Services and Mental Health Administration

No identified ongoing HSMHA supported research activities are related directly to this area.

2.8.G Sarcoid and Granulomatous Lung Diseases--
National Aeronautics and Space Administration

No identified ongoing NASA supported research activities are related directly to this area.

2.8.H Sarcoid and Granulomatous Lung Diseases--
National Science Foundation

No identified ongoing NSF supported research activities are directly related to this area.

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2.8.I Sarcoid and Granulomatous Lung Diseases--Social and Rehabilitation Service

No identified SRS supported research and/or rehabilitative activities are related directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

2.8.J Sarcoid and Granulomatous Lung Diseases--Social Security Administration

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.8.K Sarcoid and Granulomatous Lung Diseases--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.8.L Sarcoid and Granulomatous Lung Diseases--Veterans Administration

No identified ongoing VA conducted research activities are related directly to this area.

2.9 HYPERSENSITIVITY LUNG DISEASES

2.9.A Hypersensitivity Lung Diseases--Department of Agriculture

No identified ongoing USDA supported research activities are related directly to this area.

2.9.B Hypersensitivity Lung Diseases--Atomic Energy Commission

No identified ongoing AEC supported research activities are related directly to this area.

2.9.C Hypersensitivity Lung Diseases--Department of Defense

No identified ongoing DOD supported research activities are related directly to this area.

2.9.D Hypersensitivity Lung Diseases--Environmental Protection Agency

No identified ongoing EPA supported research activities are related directly to this area.

2.9.E Hypersensitivity Lung Diseases--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

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2.9.F Hypersensitivity Lung Diseases--Health Services and Mental Health Administration

HSMHA activities related to this area are included under general programs listed under 2.3.F and 2.4.F.

2.9.G Hypersensitivity Lung Diseases--National Aeronautics and Space Administration

No identified ongoing NASA supported research activities are related directly to this area.

2.9.H Hypersensitivity Lung Diseases--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

2.9.I Hypersensitivity Lung Diseases--Social and Rehabilitation Service

No identified SRS supported research and/or rehabilitative activities are related directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

2.9.J Hypersensitivity Lung Diseases--Social Security Administration

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.9.K Hypersensitivity Lung Diseases--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.9.L Hypersensitivity Lung Diseases--Veterans Administration

No identified ongoing VA conducted research activities are related directly to this area.

2.10 PULMONARY VASCULAR DISEASE

2.10.A Pulmonary Vascular Disease--Department of Agriculture

The USDA funds and administers/or conducts research related to this area (FY 72: two projects, no funding data available):

- Sustained Pulmonary Hypertension in the Newborn. The objectives of this study are: to create a model for the study of sustained pulmonary hypertension in the newborn calf, and to study the pathophysiologic changes related to this condition in the calf.
- Regional Lung Perfusion and Pulmonary Hypertension. The objectives of this study are: to study adaptation to altitude, the role of the chemoreceptors in hypoxic ventilatory drive, pulmonary hypertension, and the concomitant alterations in regional lung perfusion.

2.10.B Pulmonary Vascular Disease--Atomic Energy Commission

For description of related research activities supported by AEC, see Section 2.2.B.

2.10.C Pulmonary Vascular Disease--Department of Defense

The Department of the Army conducted one in-house research project whose purpose was the development and characterization of models to study acute mountain sickness and high altitude pulmonary edema (FY 72: one project, $150,700). Others are in development, designed to study: (1) the etiology of acute mountain sickness and high altitude pulmonary edema; (2) symptomatology of these conditions;

(3) related functional deficits and disabilities; and
(4) factors affecting recovery.

The Department of the Air Force has evaluated the effects provided by membrane oxygenators on pulmonary artery resistance and pulmonary blood flow (FY 72: one project, $4,335).

2.10.D Pulmonary Vascular Disease--Environmental Protection Agency

No identified ongoing EPA supported research efforts are related directly to this area.

2.10.E Pulmonary Vascular Disease--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

2.10.F Pulmonary Vascular Disease--Health Services and Mental Health Administration

No identified ongoing HSMHA supported research activities are directly related to this area.

2.10.G Pulmonary Vascular Disease--National Aeronautics and Space Administration

No identified ongoing NASA supported research activities are related directly to this area.

2.10.H Pulmonary Vascular Disease--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

2.10.I Pulmonary Vascular Disease--Social and Rehabilitation Service

No identified SRS supported research and/or rehabilitative activities are related directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

2.10.J Pulmonary Vascular Disease--Social Security Administration

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.10.K Pulmonary Vascular Disease--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.10.L Pulmonary Vascular Disease--Veterans Administration

One project described under Section 2.3.L (Emphysema and Chronic Bronchitis) is applicable, i.e., "Effects of Inhalation Therapy and Long-Term Follow-Up on the Course of Chronic Obstructive Lung Disease." (No information on FY 72 funding was available for this report.) The project is supported as part of the intramural research and patient care activities in VA hospitals and clinics.

2.11 HYALINE MEMBRANE DISEASE OF THE NEWBORN

2.11.A Hyaline Membrane Disease of the Newborn--Department of Agriculture

No identified ongoing USDA supported research activities are related directly to this area.

2.11.B Hyaline Membrane Disease of the Newborn--Atomic Energy Commission

The AEC funds and administers a contract supported study in this area (FY 72: one offsite contract, totalling $30,000). At Vanderbilt University, research is in progress on the time of occurrence of intraventricular hemorrhage in the newborn.

2.11.C Hyaline Membrane Disease of the Newborn--Department of Defense

In FY 72, the Department of the Air Force funded (at approximately $12,000) one in-house study entitled "Induction of the Pulmonary Surfactant in the Fetal Primate by the Intrauterine Administration of Corticosteroids." The purpose of this investigation is to evaluate the effect of prednisone on pulmonary development of the fetal rhesus monkey. The study is designed to determine if maturation of the surfactant systems is enhanced (since a deficiency of the pulmonary surfactant is a major factor in the pathogenesis of infantile respiratory distress syndrome).

2.11.D Hyaline Membrane Disease of the Newborn--Environmental Protection Agency

No identified ongoing EPA supported efforts are related directly to this area.

2.11.E Hyaline Membrane Disease of the Newborn--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

2.11.F Hyaline Membrane Disease of the Newborn--Health Services and Mental Health Administration

For a description of related research activities supported by HSMHA, see Section 2.4.F.

2.11.G Hyaline Membrane Disease of the Newborn--National Aeronautics and Space Administration

No identified ongoing NASA supported research activities are related directly to this area.

2.11.H Hyaline Membrane Disease of the Newborn--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

2.11.I Hyaline Membrane Disease of the Newborn--Social and Rehabilitation Service

No identified SRS supported research and/or rehabilitative activities are related directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

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2.11.J Hyaline Membrane Disease of the Newborn--Social Security Administration

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.11.K Hyaline Membrane Disease of the Newborn--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.11.L Hyaline Membrane Disease of the Newborn--Veterans Administration

No identified ongoing VA conducted research activities are related directly to this area.

2.12 CYSTIC FIBROSIS

2.12.A Cystic Fibrosis--Department of Agriculture

No identified ongoing USDA supported research activities are related directly to this area.

2.12.B Cystic Fibrosis--Atomic Energy Commission

No identified ongoing AEC supported research efforts are related directly to this area.

2.12.C Cystic Fibrosis--Department of Defense

No identified ongoing DOD supported research activities are related directly to this area.

2.12.D Cystic Fibrosis--Environmental Protection Agency

No identified ongoing EPA supported research activities are related directly to this area.

2.12.E Cystic Fibrosis--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

2.12.F Cystic Fibrosis--Health Services and Mental Health Administration

For description of related research activities supported by HSMHA, see Section 2.4.F.

2.12.G Cystic Fibrosis--National Aeronautics and Space Administration

No identified ongoing NASA supported research activities are related directly to this area.

2.12.H Cystic Fibrosis--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

2.12.I Cystic Fibrosis--Social and Rehabilitation Service

No identified SRS supported research and/or rehabilitative activities are related directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

2.12.J Cystic Fibrosis--Social Security Administration

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.12.K Cystic Fibrosis--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.12.L Cystic Fibrosis--Veterans Administration

No identified ongoing VA conducted research activities are related directly to this area.

2.13 ACUTE AND CHRONIC RESPIRATORY FAILURE

2.13.A Acute and Chronic Respiratory Failure-- Department of Agriculture

No identified ongoing USDA supported research activities are related directly to this area.

2.13.B Acute and Chronic Respiratory Failure-- Atomic Energy Commission

See description of AEC research in nuclear medicine technology presented in Section 2.2.B, Environmental Lung Diseases.

2.13.C Acute and Chronic Respiratory Failure-- Department of Defense

No identified ongoing DOD supported research activities are related directly to this area.

2.13.D Acute and Chronic Respiratory Failure-- Environmental Protection Agency

No identified ongoing EPA supported research activities are related directly to this area.

2.13.E Acute and Chronic Respiratory Failure-- Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

2.13.F Acute and Chronic Respiratory Failure--Health Services and Mental Health Administration

For description of related research activities supported by HSMHA, see Section(s) 2.3.F and 2.4.F.

2.13.G Acute and Chronic Respiratory Failure--National Aeronautics and Space Administration

See Section 2.1.G for description of NASA activities relevant to this area.

2.13.H Acute and Chronic Respiratory Failure--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

2.13.I Acute and Chronic Respiratory Failure--Social and Rehabilitation Service

No identified SRS supported research and/or rehabilitative activities are related directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

2.13.J Acute and Chronic Respiratory Failure--Social Security Administration

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.13.K Acute and Chronic Respiratory Failure--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.13.L Acute and Chronic Respiratory Failure--Veterans Administration

For description of related research activities supported by VA, see Section 2.3.L.

2.14 EXTRAPULMONARY MANIFESTATIONS OF RESPIRATORY DISEASES

2.14.A Extrapulmonary Manifestations of Respiratory Diseases--Department of Agriculture

No identified ongoing USDA supported research activities are related directly to this area.

2.14.B Extrapulmonary Manifestations of Respiratory Diseases--Atomic Energy Commission

See description of AEC research in nuclear medicine technology presented in Section 1.2.B, Coronary Heart Disease.

2.14.C Extrapulmonary Manifestations of Respiratory Diseases--Department of Defense

No identified ongoing DOD supported research activities are related directly to this area.

2.14.D Extrapulmonary Manifestations of Respiratory Diseases--Environmental Protection Agency

No identified ongoing EPA supported research activities are related directly to this area.

2.14.E Extrapulmonary Manifestations of Respiratory Diseases--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

2.14.F Extrapulmonary Manifestations of Respiratory Diseases--Health Services and Mental Health Administration

No identified ongoing HSMHA supported research activities are related directly to this area.

2.12.G Extrapulmonary Manifestations of Respiratory Diseases--National Aeronautics and Space Administration

The Biomedical Research Division, NASA, funds and administers a contract-supported study entitled "Long-Term Effects of Increased Ambient CO_2" (FY 72: one contract, totalling $48,000).

This is a multiphased study of CO_2-O_2 interactions in chronic acclimatization of respiratory and brain circulatory control. (It has become clear that abruptly increased or slowly increasing levels of inspired carbon dioxide tension will remain a factor limiting performance, safety or operational success both in orbiting workshop and space station missions.)

Most critical to the future understanding of acute and chronic adaptation to the environmental CO_2 stress is an analysis of respiratory brain circulatory control. An accurate descriptive model of the interplay of factors in brain circulatory control will be devised using information concerning cerebral circulatory regulation, blood gas transport, and pulmonary ventilation.

There are two areas of research interest pertaining to environmental CO_2 stress upon thermoregulation: (1) metabolic

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effects of hypercapnia are being studied in cold-adapted dogs to determine if CO_2 inhibits nonshivering thermogenesis, (2) the effect of hypercapnia upon central thermoregulatory mechanisms in which thermistor probes will be placed in the hypothalmus area of dogs having a set level of hypercapnia and varying cold stress.

2.14.H Extrapulmonary Manifestations of Respiratory Diseases--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

2.14.I Extrapulmonary Manifestations of Respiratory Diseases--Social and Rehabilitation Service

No identified SRS supported research and/or rehabilitative activities are related directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

2.14.J Extrapulmonary Manifestations of Respiratory Diseases--Social Security Administration

The SSA provides third party payments for provision of care (which may involve participation in clinical research).

2.14.K Extrapulmonary Manifestations of Respiratory Diseases--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

2.14.L Extrapulmonary Manifestations of Respiratory Diseases--Veterans Administration

No identified ongoing VA conducted research activities are related directly to this area.

III. BLOOD DISEASES

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III. BLOOD DISEASES

This section summarizes activities supported in FY 72* by the agencies represented on the Interagency Technical Committee (IATC) exclusive of the National Institutes of Health (NIH) in seven (7) categories:

- Hemophilia and Other Bleeding Disorders (3.1)
- Arterial Thromboembolism (3.2)
- Disorders of Hemostasis Due to Platelet Abnormalities (3.3)
- Venous Thrombosis and Pulmonary Embolism (3.4)
- Thromboembolism in Relation to Prosthetic Devices (3.5)
- Microcirculatory Thrombosis (3.6)
- Hemoglobinopathies (3.7).

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* Except for EPA; its data is for FY 73, the first full year of EPA operation.

3.1 HEMOPHILIA AND OTHER BLEEDING DISORDERS

3.1.A Hemophilia and Other Bleeding Disorders--Department of Agriculture

The USDA funds and administers/or conducts research in this area (FY 72: one project, no funding data available).

- Canine Hemophilia Resource Colony. This colony has functioned as a resource colony since February 1, 1968 under NIH Grant FR00412-01. The project has and is providing "healthy" beagles homozygous and heterozygous for the hemophilic genes to qualified investigators for the study of decreased Factor VIII activity and related blood clotting disorders.

3.1.B Hemophilia and Other Bleeding Disorders--Atomic Energy Commission

Activity described in 3.2.B (studies of Factor XI) is related to this area.

3.1.C Hemophilia and Other Bleeding Disorders--Department of Defense

In FY 72, the Department of the Army funded and administered one project in this area (supported at $12,400). This project, "Coagulation Abnormalities in Thermally Injured Soldiers," was designed to ascertain the clotting factor changes with time following uncomplicated thermal injury and to evaluate departures from these expected "norms" in burn patients with hemorrhagic complications.

3.1.D Hemophilia and Other Bleeding Disorders--Environmental Protection Agency

No identified ongoing EPA supported efforts are related directly to this area.

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3.1.E Hemophilia and Other Bleeding Disorders--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

3.1.F Hemophilia and Other Bleeding Disorders--Health Services and Mental Health Administration

No identified ongoing HSMHA supported activities are related directly to this area.

3.1.G Hemophilia and Other Bleeding Disorders--National Aeronautics and Space Administration

No identified ongoing NASA supported activites are related directly to this area.

3.1.H Hemophilia and Other Bleeding Disorders--National Science Foundation

The NSF funds and administers research related to this area:

- Research Initiation--Red Blood Cell Permeability in Shear Fields (See Section 3.7.H for topic description.)
- Study of Thixotropic Behavior of Blood (See Section 3.7.H for topic description.)
- Red Blood Cell Membrane Strain and Cell Permeability (See Section 3.7.H for topic description.)

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3.1.I Hemophilia and Other Bleeding Disorders--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitative activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

3.1.J Hemophilia and Other Bleeding Disorders--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

3.1.K Hemophilia and Other Bleeding Disorders--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

3.1.L Hemophilia and Other Bleeding Disorders--Veterans Administration

No identified ongoing VA conducted research activities are related directly to this area.

3.2 ARTERIAL THROMBOEMBOLISM

3.2.A Arterial Thromboembolism--Department of Agriculture

No identified ongoing USDA supported research activities are related directly to this area.

3.2.B Arterial Thromboembolism--Atomic Energy Commission

The AEC funds and administers contract supported studies in this area (FY 72: three onsite contracts, $220,000; two contracts, $76,000).

- At the Franklin McLean Memorial Research Institute (University of Chicago), investigators have isolated bovine Factor XI in a high state of purity and are studying its structure and properties. Effects of pure Factor XI on clotting activity in plasma samples from patients with various types of clotting deficiencies have been evaluated. The amino acid sequence of Factor XI is currently being elucidated and its interaction with Factor IX is under study. An attempt to purify Factor IX is planned. Studies with human activated Factor XI indicated that its binding site for diisopropylphosphofluoridate is identical with the same region of the thrombin and trypsin molecules. Other research by the Chicago investigators is concerned with the use of a bacterial heparinase to remove exogenous heparin from blood samples (samples from patients on heparin therapy) prior to laboratory testing of clotting activity.

- Investigators at Brown University, Johns Hopkins University, and the Oak Ridge National Laboratory (Biology Division) are using a variety of physical, chemical, and biological techniques to study both normal and abnormal platelets. This effort includes research on the sequence of events occurring in the differentiation of the megakaryocyte into the plate- regulation of platelet production and homeostasis, platelet turnover and kinetics, identification and isolation of thrombopoietin, platelet ultrastructure and metabolism, function of the platelet outer

membrane, mechanism of platelet adhesion and the early phase of the release reaction, and platelet abnormalities associated with the Wiskott-Aldrich syndrome. (Note - AEC support of this research on blood platelets in FY 72 accounted for $180,000 of the $296,000 total allocated to work in this section. Of the $180,000, $104,000 were allocated to one onsite contractor with the balance supporting two offsite contracts.)

- Research at the University of Rochester has demonstrated that iodine-131-labeled antibody to human fibrinogen concentrates in most human thrombi, where it can be detected by external scintillation scanning. Iodine-131-labeled preparations of human fibrinogen and rabbit antibodies to human fibrinogen are currently being tested as diagnostic agents for the detection of deep venous thrombi in various parts of the body, as well as atrial thrombi secondary to mitral valve disease.

3.2.C Arterial Thromboembolism--Department of Defense

No identified ongoing DOD supported research activities are related directly to this area.

3.2.D Arterial Thromboembolism--Environmental Protection Agency

No identified ongoing EPA supported research activities are related directly to this area.

3.2.E Arterial Thromboembolism--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

3.2.F Arterial Thromboembolism--Health Services and Mental Health Administration

No identified ongoing HSMHA supported research activities are related directly to this area.

3.2.G Arterial Thromboembolism--National Aeronautics and Space Administration

No identified ongoing NASA supported research activities are related directly to this area.

3.2.H Arterial Thromboembolism--National Science Foundation

For project titles of related research activities supported by NSF, see Section 3.1.H; for description of these projects see Section 3.7.H.

3.2.I Arterial Thromboembolism--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitative activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

3.2.J Arterial Thromboembolism--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

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3.2.K Arterial Thromboembolism--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

3.2.L Arterial Thromboembolism--Veterans Administration

No identified ongoing VA conducted research activities are related directly to this area.

3.3 DISORDERS OF HEMOSTASIS DUE TO PLATELET ABNORMALITIES

3.3.A Disorders of Hemostasis Due to Platelet Abnormalities--Department of Agriculture

The USDA funds and administers a study related to this area (FY 72: one project, funding data not available).

- Biochemical Mechanisms Related to Hemostasis in Swine and Other Animals. In this work the mechanisms of hemostasis are being studied, particularly platelet properties, in an attempt to elucidate the defects in bleeder swine. These bleeder animals are research models used to gain information that may have a broader application in other species and may be useful in the eventual development of therapeutic measures in human thrombotic and hemorrhagic diseases.

3.3.B Disorders of Hemostasis Due to Platelet Abnormalities--Atomic Energy Commission

The AEC funds and administers contract supported studies related to this area (FY 72: one onsite contract, $104,000; two offsite contracts, $76,000). This work, a study of both normal and abnormal platelets, is also described in Section 3.2.B, Arterial Thromboembolism. The research includes studies of: 1) the complete sequence of events in the differentiation of the megakaryocyte into the platelet; 2) regulation of platelet production and homeostasis; 3) platelet turnover and kinetics; 4) identification and isolation of thrombopoietin; 5) platelet ultrastructure and metabolism; 6) function of the platelet outer membrane; 7) mechanism of platelet adhesion and the early phase of the release reaction; and 8) platelet abnormalities associated with the Wiscott-Aldrich syndrome.

3.3.C Disorders of Hemostasis Due to Platelet Abnormalities--Department of Defense

No identified ongoing DOD supported research activities are related directly to this area.

3.3.D Disorders of Hemostasis Due to Platelet Abnormalities--Environmental Protection Agency

No identified ongoing EPA supported research activities are related directly to this area.

3.3.E Disorders of Hemostasis Due to Platelet Abnormalities--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

3.3.F Disorders of Hemostasis Due to Platelet Abnormalities--Health Services and Mental Health Administration

No identified ongoing HSMHA supported research activities are related directly to this area.

3.3.G Disorders of Hemostasis Due to Platelet Abnormalities--National Aeronautics and Space Administration

No identified ongoing NASA supported research activities are related directly to this area.

3.3.H Disorders of Hemostasis Due to Platelet Abnormalities--National Science Foundation

No identified ongoing NSF supported research activities are related directly to this area.

3.3.I Disorders of Hemostasis Due to Platelet Abnormalities--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitative activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

3.3.J Disorders of Hemostasis Due to Platelet Abnormalities--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

3.3.K Disorders of Hemostasis Due to Platelet Abnormalities--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

3.3.L Disorders of Hemostasis Due to Platelet Abnormalities--Veterans Administration

The VA funds, conducts and administers numerous studies related to disorders of hemostasis due to platelet abnormalities. The following paragraphs describe those studies for which

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information was available (no information on FY 72 funding was available for this report). The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics.

- Thrombocytopenia Studies. At the VA, studies have been conducted of patients whose thrombocytopenia is due to an antigenetic drug metabolite, and were able to isolate the responsible antigen from the urine of a patient with thrombocytopenia related to acetaminophen ingestion.

  Studies of two patients with heterophile positive infectious mononucleosis have revealed an anti-platelet antibody dependent on the presence of an EB virus antigen. These results provide a model for the study of the role of viral antigen in the etiology of acute idiopathic thrombocytopenic purpura.

- Platelet Studies: Membrane Abnormalities in Iron Deficiency and Evaluation of Specific Acid Phosphotase Isozymes. A qualitative platelet defect has been found in iron deficient rats. These platelets show poor recovery from hypotonic stress and have an abnormal response to adenosine diphosphate. These defects are corrected by giving iron to the animals. The hemostatic sufficiency of these findings is under study but it has been observed that these iron deficient rats bleed more readily than normal rats and there has been a long-standing clinical impression that iron deficient patients have a bleeding tendency. Further studies are planned to evaluate the exact biochemical defect in these "iron deficient" platelets.

3.4 VENOUS THROMBOSIS AND PULMONARY EMBOLISM

3.4.A Venous Thrombosis and Pulmonary Embolism--Department of Agriculture

No identified ongoing USDA supported research activities are related directly to this area.

3.4.B Venous Thrombosis and Pulmonary Embolism--Atomic Energy Commission

The AEC funds and administers contract supported studies related to this area. See Section 3.2.B, Arterial Thromboembolism, for pertinent topic descriptions. See also the discussion of the AEC program in nuclear medicine technology (Section 2.2.B, Environmental Respiratory Diseases), which includes research (at the University of California, Los Angeles) on the development of improved methods of lung scanning for diagnostic use in patients with suspected pulmonary embolism. Xenon-133, ^{99m}Tc-albumin aerosol, and ^{131}I-MAA are being tested in animals as potential diagnostic agents.

3.4.C Venous Thrombosis and Pulmonary Embolism--Department of Defense

No identified ongoing DOD supported research activities are directly related to this area.

3.4.D Venous Thrombosis and Pulmonary Embolism--Environmental Protection Agency

No identified ongoing EPA supported research activities are related directly to this area.

3.4.E Venous Thrombosis and Pulmonary Embolism--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment.

3.4.F Venous Thrombosis and Pulmonary Embolism--Health Services and Mental Health Administration

RMPS has supported one program in the emergency treatment of pulmonary embolism at the Marshfield Clinic, Marshfield, Wisconsin, under the auspices of the Wisconsin RMP (FY 72 support $55,400).

3.4.G Venous Thrombosis and Pulmonary Embolism--National Aeronautics and Space Administration

No identified ongoing NASA supported research activities are related directly to this area.

3.4.H Venous Thrombosis and Pulmonary Embolism--National Science Foundation

For listing of additional related research activities supported by NSF, see Section 3.1.H and for description of these research projects, see Section 3.7.H.

3.4.I Venous Thrombosis and Pulmonary Embolism--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitative activities relate directly to this area.

The SRS provides third party payments for provision of care (which may involve participation in clinical research).

3.4.J Venous Thrombosis and Pulmonary Embolism--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

3.4.K Venous Thrombosis and Pulmonary Embolism--Department of Transportation

No identified ongoing DOT supported research activities are related directly to this area.

3.4.L Venous Thrombosis and Pulmonary Embolism--Veterans Administration

The VA funds, conducts and/or administers numerous studies related to venous thrombosis and pulmonary embolism. The following paragraphs describe those studies for which information was available. (No information on FY 72 funding was available for this report.) The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics.

- Transvenous Approach to Pulmonary Embolism. There has been a great need for a device which can be introduced through a peripheral vein and be advanced into the inferior vena cava so that

it can prevent the passage of blood clots up the inferior vena cava as a source of pulmonary emboli. A new device has been constructed which will completely collapse within a small tube and then spring open when positioned in the inferior vena cava. In VA studies with the dog, this device has been highly successful in trapping large pulmonary emboli while remaining patent so that blood will still flow through this important blood vessel.

It is hoped that such a device can be introduced through peripheral veins of patients having a high surgical risk whose lives are threatened through repeated pulmonary emboli. (Since the introduction of such devices is a procedure which can be performed at the bedside, this procedure has a high potential for helping many patients who otherwise could not be treated.)

- Control Study of Thrombolitic Therapy in the Treatment of Deep Venous Thrombosis. This project represents a controlled trial in which the relative merits of heparin, a clot-preventing agent, are matched against those of streptokinase, a clot-dissolving agent. Only patients with fully documented venous thrombosis are included and these are assigned to either of the treatment groups (heparin or streptokinase) by random selection. To date 28 patients have been included in this study. Of these, 11 have been treated with heparin and 17 with streptokinase. The results of the study clearly suggest that streptokinase is superior to heparin in the treatment of this disease. Clot dissolution with restoration to normal venous anatomy has been observed in 40 percent of the streptokinase group and in 5 percent of the heparin group. Since venous thrombosis has a high incidence in the aging veteran patient, the establishment of the value of streptokinase treatment will be an important contribution to patient care. The inclusion of larger numbers of patients in this study will help to reach this goal.

3.5 THROMBOEMBOLISM IN RELATION TO PROSTHETIC DEVICES

3.5.A Thromboembolism in Relation to Prosthetic Devices--Department of Agriculture

No identified ongoing USDA supported research is directly related to this area.

3.5.B Thromboembolism in Relation to Prosthetic Devices--Atomic Energy Commission

See description of AEC research on the chemical synthesis of new blood-compatible polymers (Section 1.3.B, Peripheral Vascular Disease).

3.5.C Thromboembolism in Relation to Prosthetic Devices--Department of Defense

No identified ongoing DOD supported efforts are directly related to this area.

3.5.D Thromboembolism in Relation to Prosthetic Devices--Environmental Protection Agency

No identified ongoing EPA supported efforts are related directly to this area.

3.5.E Thromboembolism in Relation to Prosthetic Devices--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

3.5.F Thromboembolism in Relation to Prosthetic Devices--Health Services and Mental Health Administration

No identified ongoing HSMHA supported activities are related directly to this area.

3.5.G Thromboembolism in Relation to Prosthetic Devices--National Aeronautics and Space Administration

No identified ongoing NASA supported activities are related directly to this area.

3.5.H Thromboembolism in Relation to Prosthetic Devices--National Science Foundation

No identified ongoing NSF supported activities are related directly to this area.

3.5.I Thromboembolism in Relation to Prosthetic Devices--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitative activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

3.5.J Thromboembolism in Relation to Prosthetic Devices--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

3.5.K Thromboembolism in Relation to Prosthetic Devices--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

3.5.L Thromboembolism in Relation to Prosthetic Devices--Veterans Administration

No identified ongoing VA conducted research activities are related directly to this area.

3.6 MICROCIRCULATORY THROMBOSIS

3.6.A Microcirculatory Thrombosis--Department of Agriculture

No identified ongoing USDA supported research is directly related to this area.

3.6.B Microcirculatory Thrombosis--Atomic Energy Commission

For description of related research activities supported by AEC, see Section 3.2.B.

3.6.C Microcirculatory Thrombosis--Department of Defense

No identified ongoing DOD supported efforts are directly related to this area.

3.6.D Microcirculatory Thrombosis--Environmental Protection Agency

No identified ongoing EPA supported efforts are related directly to this area.

3.6.E Microcirculatory Thrombosis--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

3.6.F Microcirculatory Thrombosis--Health Services and Mental Health Administration

No identified ongoing HSMHA supported activities are related directly to this area.

3.6.G Microcirculatory Thrombosis--National Aeronautics and Space Administration

No identified ongoing NASA supported activities are related directly to this area.

3.6.H Microcirculatory Thrombosis--National Science Foundation

For listing of related research activities supported by NSF, see Section 3.1.H; for description of these research projects see Section 3.7.H.

3.6.I Microcirculatory Thrombosis--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitative activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

3.6.J Microcirculatory Thrombosis--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

3.6.K Microcirculatory Thrombosis--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

3.6.L Microcirculatory Thrombosis--Veterans Administration

No identified ongoing VA conducted research activities are related directly to this area.

3.7 HEMOGLOBINOPATHIES

3.7.A Hemoglobinopathies--Department of Agriculture

No identified ongoing USDA supported research is directly related to this area.

3.7.B Hemoglobinopathies--Atomic Energy Commission

The AEC funds and administers contract supported studies related to this area (FY 72: four onsite contracts, $496,000; two offsite contracts, totalling $568,000):

- At the Oak Ridge National Laboratory (Biology Division), variant forms of hemoglobin polypeptide chains have been characterized in several strains of mice. Amino acid sequences have been elucidated and electrophoretic mobilities have been explained. Present work is addressed to the determination of error frequencies and the estimation of production of somatic mutations (base substitutions) in the hemoglobin chains.

- Investigators at the New York Blood Center have developed a radioisotopic assay which can be used to measure rates at which each of the six hemoglobin variants in the circulating rat erythrocytes are synthesized. Previous work has demonstrated that each hemoglobin polymorph is synthesized in erythroid cells of different ages. The assay is now being used to study endogenous and exogenous factors that influence the synthesis of the different hemoglobin variants in erythroid tissue.

- The red cell membrane is being studied by a number of AEC contractors. At the Lawrence Livermore Laboratory, research is directed to the study of the quaternary structure (subunit array) and amino acid sequences of proteins in the erythrocyte membrane. Protein-lipid and protein-protein interactions are being investigated. The role in alkali metal transport of a specific protein that binds monovalent cations is also under study. In other research at the Livermore facility, a detailed chemical analysis

of lipids present in the red cell membrane is being conducted in a number of mammalian species. Investigators at the Franklin McLean Memorial Research Institute are studying the chemistry and biochemistry of lipid components in the red cell membrane. Present work centers on the identification of different sphingomyelin species and the possible lability of choline methyl groups in membrane phospholipids. In research at Harvard University, biochemical and biophysical techniques are being used in a comprehensive study of the functional role of the erythrocyte membrane in transport processes. A detailed model of the membrane has been constructed and is refined as new information emerges. Research at the University of Rochester deals with the functional implication of normal and altered contractile proteins in the red cell membrane. The role of sulfhydryl groups in the normal and pathologic erythrocyte is also under study at Rochester.

3.7.C Hemoglobinopathies--Department of Defense

In FY 72 the Department of Army sponsored two studies (funded at $77,000) in this area. These studies were designed to: (1) examine the catalytic chemistry and oxygen transport capability of red blood cells and the effects of concurrent platelet damage and/or fibrin formation on erythrocyte morphology so as to clarify the mechanisms of hemolysis associated with damaged blood resulting from wounds; (2) to determine the effects of erythrocyte intermediates on oxygen dissociation properties of hemoglobin; and (3) to investigate the various membrane-bound adenosine triphosphatases, intracellular hexokinase activity, the level of 2,3-diphosphoglyceric acid, and the overall glucose-to-lactate conversion.

3.7.D Hemoglobinopathies--Environmental Protection Agency

The EPA funds and administers three studies of the occurrence of methemoglobinemia:

- In preschool children consuming a high nitrate water (from 100-400 mg/L as NO_3) (FY 72: approximately $10,000) (An increase of methemoglobin content in blood with increasing dosage of nitrate has been demonstrated.)
- A P.L. 480 study in Yugoslavia, "Epidemiologic Study of Methemoglobinemia in Croatia" (FY 73: $70,000) (Infants less than six months who are exposed to high nitrate water are being studied.)
- A P.L. 480 study, "Health Effects of Nitrates in Israel" (FY 73: $66,600) designed to determine incidence of methemoglobinemia in a study population in the Gaza Strip.

3.7.E Hemoglobinopathies--Food and Drug Administration

No identified ongoing FDA supported research activities are related directly to this area. The FDA has responsibility for the monitoring and the approval of the development and testing of new drugs which may be used in research and treatment in this area.

3.7.F Hemoglobinopathies--Health Services and Mental Health Administration

The Sickle Cell Disease Office in the National Center for Family Planning is supporting 19 sickle cell screening and education clinics under reimbursement from NHLI. Efforts are

also devoted to dissemination of information and to education about sickle cell disease. Total funding for the clinics in FY 72 was $1,900,000.*

3.7.G Hemoglobinopathies--National Aeronautics and Space Administration

The Biomedical Research Division, NASA, funds and administers research programs in this area (FY 72: two contracts, totalling $40,000).

These studies fall into the following categories: red blood cell metabolism; erythrocyte membrane structure; and hemoglobin synthesis, structure and function. These studies include:

- Membrane Characterization by Micromethods (FY 72: one contract, $25,000). The objective of this study is to examine experimentally the effects of breathing mixture constituent gases on:
  - The physical confirmation of hemoglobin and of bioplymer in erythrocyte membranes
  - The stability of the organized water in the hydration sheaths of these molecules as a function of pN_2. The ultimate objective is to develop the proposed methodology to the point where:
    - It can be used as a definitive evaluation of individual gases and gas mixtures for their acceptability for spacecraft use
    - It can be used to define the safe tolerance for variations in partial pressure of constituent gases in breathing mixtures as a function of operating pressure.

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* Also carried in NHLI FY 72 dollar totals. See Volume V, Part I, Program Analysis: National Heart and Lung Institute.

- Analysis of Antilipid Oxident Properties of Plasma and Red Cell Membranes (FY 72: one contract, $15,000). The objectives of this effort are to:

  - Evaluate the protective effect of Vitamin E relative to red cell damage by high concentrations of oxygen

  - Determine the effects of oxygen on heme metabolism and synthesis relative to red cell production. These data will further elucidate the mechanisms by which oxygen causes irreversible damage to circulating red cells resulting in a decrease in the total red cell mass.

3.7.H Hemoglobinopathies--National Science Foundation

The NSF funded and administered 19 projects (FY 72 funding, $503,200) related to the biophysics, biology and mechanics of blood.

- Hemoglobin Structure and Ligand Equilibria. Present knowledge of the three-dimensional structure of hemoglobin, although remarkably complete, does not yet fully account for three distinctive features of the equilibria between hemoglobin and different ligands which are:

  - The relatively low affinity of hemoglobin for ligands such as oxygen

  - The sigmoid shape of the ligand equilibrium curves

  - The effect of pH upon ligand equilibrium.

  Investigations are continuing on these and include:

  - Extending the study of oxidation reduction systems to additional varieties of hemoglobin

  - Studying the reactions and equilibria of intact and modified ferri- and ferrohemoglobins with appropriate ligands

- Working on the molecular structure of the hemoglobin tetramers in solution and the dissociation into halves or quarters, as influenced by ligand equilibria and by various reagents.

- Relations Between Structure and Function in Hemoglobins, Myoglobins, and Related Substances. Research is being conducted on the physical properties and behavior of hemoglobin, myoglobin and various related substances among them hemocyanins, hemrythrins and several enzymes. The central theme of the study is the understanding of the conformational changes associated with ligand-binding by large working proteins.

- Quaternary Interactions in Proteins. A research program is being conducted for the study of quaternary interactions in proteins and the development of necessary technical methods. The functional aspects of the subunit structure of hemoglobin and the ATPase of mitochondria are considered in detail. Experiments are proposed at a subtle, but critical level concerning the exact description of the dissociation of deoxyhemoglobin, the dissociation constant for half-saturated hybrid hemoglobins and the variation in dissociation constant with degree of ligand binding.

- Kinetics of the Quaternary Structural Transition of Hemoglobin. The objective of this research is to measure the kinetics of the structural transition which hemoglobin undergoes subsequent to the sudden removal of ligand. The influence of the following factors will be investigated:

  - The chemical structure of the heme group

  - Modification of some amino acid residues in the interface between the subunits

  - Changes in pH, ionic strength, and polyphosphates

  - The oxidation state of the heme groups or chains on the reactivity of the partner chains within the intact tetramer.

- Ligand Binding and Protein Disaggregation Properties of Methemoglobin. The disaggregation behavior of tetrameric human methemoglobin A is being studied by sedimentation equilibrium. The thermodynamic parameters governing this process, and also, the ligand binding properties of the various possible protein aggregates will be determined.

  The kinetics of ligand binding to the heme iron will be measured, and compared with equilibrium binding results in an attempt to elucidate the mechanism of the overall reaction. The effect of protein dissociation on the mechanism will also be investigated.

  Finally, the disaggregation behavior of carboxyhemoglobin will be studied. It is hoped to establish a criterion for determining how similar the structures of carboxy- and methemoglobin are by comparing the thermodynamic parameters governing the dissociation of these two protein derivatives.

- Quantum Chemical Investigations of Heme Proteins, Ferredoxins Lysozyme and A Series of Muscarinic Agonists. The study is directed at characterization of the active sites of heme proteins and ferredoxins using working molecular orbital programs, particularly one called Interactive Extended Huckel Theory, and to extend the scope of the investigations by formulating a new program to calculate additional, largely spectroscopic properties of the active site of these iron-containing proteins. With the new program it should be possible to calculate such properties as zero field, quadrupole and hyperfine splittings, magnetic moments and g values in electron spin resonance and their dependence on the explicit conformational and electronic nature of the immediate environment of the iron at the active site.

- Oxygen Photolysis and Recombination Studies of Hemoproteins. The objective of this research is to use oxygen photolysis and recombination studies to determine the relationship between structure and function of ligand binding to hemoproteins, principally hemoglobin. Developmental work has been performed in the laboratory on high energy laser photolysis pulses and fast clean optical readout of

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absorption changes of hemoproteins. It is possible now for this group to work directly with the physiological ligand oxygen at neutral pH. Oxygen photolysis and recombination studies of hemoproteins will be performed.

- Immunochemistry of Cattle Blood. Study is aimed at elucidation of the chemical structure of the J glycolipid. Preliminary results indicate that this glycolipid consists of a longchain base, glucose, galactose, phosphorus, glycerol and fatty acids in the ratio of 1:1:2:1:1:3.

  Effort also will be directed at studying the protein-bound blood group active substance. The latter will be isolated and purified, and the structure of the serological determinant, the linkage to the protein and the identity of the protein will be investigated.

  Studies will also be made to determine the factors affecting the coating of the cattle cells *in vivo* and *in vitro*.

- Characterization of Active Sites in Hemoproteins. The research is concerned with identifying and characterizing the heme binding site in a number of important hemoproteins. The technique to be used is based on substitution of the iron-porphyrin in the protein with a protoporphyrin, that is a photo-sensitizer, and then subjecting the new complex to limited photoxidation. Specific destruction of photolabile residue(s) within the active site "pocket" will take place. Thus, based on the presence of an altered residue(s), a binding-site peptide(s) can be identified and then isolated for structure determination.

- The Isolation and Characterization of the Hemoglobin Messenger RNA. The objectives of this work are:

  - To continue work on the identification and purification of the hemoglobin RNA
  - To investigate its chemical and physical properties
  - To study its transport to the cytoplasm and attachment to ribosomes.

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- Structural Approach to Hemoglobin Kinetics and Function. The main objective in solving the atomic structure of a protein by the techniques of X-ray protein crystallography is the determination of the molecular basis of its functional properties. To date, mainly equilibrium properties of the protein in solution have been considered. The difficulties involved in relating kinetic properties, which depend on the difference in free energy between a stable and a transient structure, to the observable structure have not yet been faced. This proposal will consider these problems by examining hemoglobin, on which extensive structural and kinetic data, and expertise, are available at Cornell. Particular attention will be paid to the agreement, or lack of it, between the kinetic data and Perutz's current model for hemoglobin function at the molecular level. Specifically, kinetic and ultracentrifuge data suggest that the tertiary structures of ferrous and ferric liganded hemoglobins differ in small but significant detail. These differences in structure will be determined by X-ray difference Fourier techniques, which are sensitive to very small changes in structure, and related both to the kinetic and ultracentrifuge data, and to Perutz's model. The structure of some mutant human hemoglobins will be determined similarly, with the same objects in mind.

- Chemistry of the Active Site of Hemerythrin. Hemerythrin is a nonheme iron protein which serves as a reversible oxygen carrier in the red cells of the brachiopods and the sipunculids. The mechanism of the reversible oxygen binding is of great interest vis-a-vis the mechanism of hemoglobin and cytochrome oxidase binding.

  Research is continuing on completing the identification of the ligands binding iron in the active site of hemerythrin and extending the techniques used in this study to the elucidation of the subunit binding site and the strong anion binding site which is important because it may serve as a control function over ligand binding at the active site.

  Also, an investigation of the mechanism of oxygen binding to the iron site in hemerythrin is proposed.

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- Optical Activity of Biological Macromolecules in Relation to Conformation. This research program involves studies of the structural basis of optical activity of certain biologically important molecules. The work is pursued along three broad lines of investigation:

  - A study of the effects of binding of prosthetic groups on the conformation and reactivity of apoproteins--primarily devoted to hemoglobin and lipoamide dehydrogenase

  - The optical activity of cystine-containing proteins dealing mainly, but not only, with conformation and reactivity of cystine residues in human and egg-white lysozymes, a human myeloma protein; insulin and ribonuclease

  - ORD, CD and related studies of immunochemically reactive oligo- and polysaccharides.

- Determination and Differentiation of Embryonic Erythropoiesis. Several studies are underway:

  - To identify and trace the development of the precursors of the two embryonic red cell series through cloning experiments in vitro

  - To expand studies on the control of biosynthesis of macromolecules in cell cultures of early embryonic erythroid cells. Particular attention is being paid to specific hemoglobin synthesis, to the nuclear proteins and histones, and to a possible interference with differentiation by BUdR, to the nuclear RNA species and to the differentiation of the red cell surface

  - To quantitate and describe biochemically the induction of erythropoiesis in mesenchymal cells.

- Molecular Structure of the Immunoglobulin Receptor in Continuous Cultures of Diploid Human Lymphocytes. This grant supports a study of the immunoglobulin receptor sites of human lymphocyte cell surfaces. Methods are being developed for detecting and isolating these sites. The orientation of immoglobulins in the plasma membrane is also being

studied. In addition, the molecules surrounding membrane immunoglobulins are being investigated.

- Research Initiation--Red Blood Cell Permeability in Shear Fields. The membranes of red blood cells are known to be semipermeable, and transmembrane diffusion can be both passive and facilitated. It is hypothesized here that passive permeability is related to the membrane tension, and impermeable substances may penetrate the cell with increasing tension. A prelytic release of cellular substances is expected, a finding that might link clotting and red blood cell components in the absence of hemolysis.

  Membrane tensions will be applied fluid dynamically by laminar shear stresses in a circular Couette flow. Glycerol will be the initial test penetrant, with further tests utilizing greater molecular diameter homologues. Permeability effects may be important at physiological stresses due to non-linearities in the modulus of elasticity of the membrane. The modulus is expected to increase with stress and the membrane pores may be more easily "stretched" for low levels of stress.

- Study of Thixotropic Behavior of Blood. Rheological data will be obtained using blood samples of healthy adults, both male and female, and adult females on contraceptive and fertility hormonal therapy. The thixotropy of blood will be compared between these two groups by using the following parameters in a rheological model: steady state and transient viscosity coefficients under different shear rates, rate constant for dissociation of rouleaux of erythrocytes, the order of the dissociation reaction, the equilibrium constant of erythrocyte and rouleaux, and the yield stress of blood.

- Red Blood Cell Membrane Strain and Cell Perinability. The goal of this project is to determine the relationships between magnitude and duration of red blood cell membrane stress and the membrane transport processes. The cells will be kept in suspension by shear flow and by ultra-centrifugation

to avoid surface contact. The cell dimensions and shape will be measured by scanning electronmicroscopy and the transport process determinations will be accomplished by radioactive labeling techniques.

- Theory of Blood Flow. This research will investigate problems in arterial hemodynamics by means of a continuum theory which allows one to account for the presence of red cells in the blood. Theoretical results will be compared to reported experimental results with emphasis on comparisons to in vivo studies.

  The initial investigation will study vessel tapering and entrance effects for the case of blood flow in the descending thoracic aorta. A second aim will consider the effects of cell deformations in arterial hemodynamics.

3.7.I Hemoglobinopathies--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitation activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

3.7.J Hemoglobinopathies--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

3.7.K Hemoglobinopathies--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

3.7.L Hemoglobinopathies--Veterans Administration

The VA funds, conducts and administers numerous studies related to hemoglobinopathies. The following paragraphs describe those studies for which information was available. (No information on FY 72 funding was available for this report.) The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics.

- Assessment of the Influences of Sickle Cell Trait on Health and Mortality Rates. From 1964 to 1966 the medical records of more than 4,000 black patients have been surveyed to assess the influence of sickle cell trait on health and mortality rates. Although this preliminary study has suggested a relationship of the sickle cell trait to certain diseases, large scale studies are required to conclusively assess the question.

- Sickle Cell Trait--Survey of S-A and Related Hemoglobinopathies and Study of Sickling Under Various Conditions. This project was designed to determine the relationship between the number of cycles of sickling-unsickling of the erythrocytes of the sickle trait individual, mechanical fragility, and red cell survival studied by the radioactive chromium labeling method. The total research project included the epidemiologic study of sickle cell trait and clinocopathologic correlation.

- Pathogenic Significance of the Sickle Cell Trait. This study involves 15 VA hospitals, and the Cooperative Studies Biostatistical Center in the collection of data on the medical problems diagnosed during the hospitalization of black patients with and without the sickle cell trait. It is estimated that 50,000-60,000 subjects will be evaluated in order to learn whether this trait has any bearing on the general health of the affected veteran. The study should be completed in 1974.

- Hormones and Blood-Detection of Sickle Cell Hemoglobin. Several novel electrophoretic techniques have been developed at the VA for studying thyroxine building properties of low weight molecular substances--based on observing change in mobility rather than on measurement of amounts of bound substance. Evidence for thyroid hormone binding material of low-molecular weight in human serum ultrafiltrate has been found. Further, a previously unnoticed thyroid hormone binding material of high-molecular weight was also found in human serum. Screening of patients' sera continues with the object of utilizing this test for the diagnosis of thyroid and liver diseases. The same techniques are expected to be applicable to the study of drug interaction in biologic fluids.

  The technique was modified for use in the detection of sickle cell hemoglobin, and applied to test the whole patient population of this center. A minute amount of blood only is required, and 90 samples can be tested simultaneously within one hour. Over 3,000 blood samples have been tested. Twenty-six cases of sickle cell trait and 13 cases of other abnormal hemoglobins were found, the majority of them unsuspected by the patient's history. This technique is specifically suitable for mass screening purposes.

- Functional Properties of S Hemoglobin. This project is designed to study the functional properties of S Hemoglobin within the cell in terms of oxygen transport and factors which might cause a decreased affinity for oxygen.

  Since only deoxygenated S hemoglobin will sickle, one approach to therapy would be to increase the O_2 affinity of S hemoglobin making it less readily rendered oxygen-free and therefore less likely to sickle.

  Initially, this investigation focused on the effects of lowering 2,3-DPG, the specific modifier of hemoglobin function. Subsequently the carbamylation of hemoglobin by cyanate has been investigated in some detail.

- Studies on Hemoglobin and Thalassemia. Observations have been made concerning the morphological results of the molecular interactions between hemoglobins S and C and between hemoglobin S and thalassemia. Results seem to indicate that actual intraerythrocytic crystallization of hemoglobin S-C is infrequent and can be detected by electron microscopy only. Crystalline shapes seen within the erythrocytes in the syndrome most likely are precrystalline in nature. Such observations concerning the ultrastructural manifestations of molecular interaction of hemoglobins may point the way toward a rational explanation of the disease manifestations and may result in more effective therapy for the patient.

- Studies of Human and Animal Hemoglobin Variants. Four studies are being conducted:

  - Studies on the Genetic Heterogeneity of Human Fetal Hemoglobin. This problem has become more complex with the evidence that not two but perhaps as many as four nonallelic structural gamma genes are present on each chromosome. This means that in evaluating the chemical heterogeneity of this fetal protein one has to consider the activities of as many as eight gamma chain structural loci (four on each chromosome). Variability in these activities, either acquired or inherited, might explain the observations made in many congenital and hereditary disorders.

    The studies are continuing. The ultimate goal of the study is to include the activities of some (or perhaps all) gamma chain structural genes. Such an approach might lead to a stimulation of fetal hemoglobin production in various disorders, sickle cell anemia and related diseases particularly.

  - Survey of Abnormal Hemoglobins. The results of analyses show that besides the expected subjects with sickle cell trait, Hb-C trait, and other common disorders several cases with a beta-thalassemia heterozygosity and with a fetal

hemoglobin abnormality were discovered. Extensive studies on some of these patients are presently in progress.

Note: Initial data also has suggested that screening of a large population for "sickle cell" should be done by advanced techniques; a simplified methodology, promoted by many and stimulated by various commercial companies, will result in inadequate and sometimes inaccurate information and should therefore be considered potentially dangerous.

- Analysis of Hemoglobin from Anemic and Nonanemic Barbary Sheep. These analyses indicate that some silent structural loci are present which are activated during anemic states whereas in other such genes, if present, cannot be activated. This and related animal species offer excellent animal models to be used in the VA approach to influence the activities of structural genes.

- Mechanisms of Action of 2,3-Diphosphoglycerate. Due to its action in releasing oxygen from hemoglobin, and hence its importance in blood for transfusion purposes a complete understanding of 2,3-diphosphoglycerate is a fundamental necessity. Research into the mechanisms of its action have been continued using goats as the experimental animals. It has been shown that the red cells of newly born goats become very acid immediately after birth. This probably is due to the increased 2,3-DPG, (which was previously demonstrated): the acid conditions in the cells probably cause a change in oxygen affinity. This is different than the human where 2,3-DPG combines directly with the hemoglobin to change the oxygen affinity. Further investigations to determine whether thyroid hormone may increase 2,3-DPG in the live animal are being undertaken.

- Effect of Fluorocarbons on Sickle Cells. Research on the effect of fluorocarbons on sickle cells has been very promising and indicates that these compounds may have some usefulness in the future with regard to patient care and the management of sickle cell anemia.

IV. BLOOD RESOURCES

IV. BLOOD RESOURCES

This section summarizes activities supported in FY 72 by the agencies* represented on the Interagency Technical Committee (IATC) exclusive of the National Institutes of Health (NIH) in six (6) categories:

- Blood Collection (4.1)
- Fractionation and Preservation (4.2)
- Laboratory Procedures and Controls (4.3)
- Utilization (4.4)
- Systems Management (4.5)
- Transplantation (4.6).

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* Except EPA; FY 73 figures are presented for EPA.

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4.1 BLOOD COLLECTION

4.1.A Blood Collection--Department of Agriculture

No identified ongoing USDA supported research is directly related to this area.

4.1.B Blood Collection--Atomic Energy Commission

As discussed under Heart and Blood Vessel Diseases (See Section 1.1.B, Atherosclerosis), AEC supported investigators are studying plasma proteins from diverse points of view. Other investigators are conducting basic studies on plasma clotting factors and the erythrocyte (See discussion in Section 3.2.B, Arterial Thromboembolism and Section 3.7.B., Hemoglobinopathies).

In addition the AEC funds and administers investigations:

- Using instrumental capabilities at the Oak Ridge National Laboratory which relate to the problem of developing new methods of collecting and aseptic processing of blood on a large scale
- Relating to the care of the blood donor, specifically focused on the effects of extensive removal of blood on the incidence of leukemia (in irradiated animals).

4.1.C Blood Collection--Department of Defense

No identified ongoing DOD supported efforts are directly related to this area.

4.1.D Blood Collection--Environmental Protection Agency

No identified ongoing EPA supported efforts are related directly to this area.

4.1.E Blood Collection--Food and Drug Administration

No identified ongoing FDA supported research efforts are directly related to this area.

4.1.F Blood Collection--Health Services and Mental Health Administration

No identified ongoing HSMHA supported activities are related directly to this area.

4.1.G Blood Collection--National Aeronautics and Space Administration

The Biomedical Research Division of NASA funds and administers a hematology program, designed to elucidate and define those physiological mechanisms, relative to the immunohematological systems, which are operative in man's adaptation to and from the spaceflight environment.

- Special Inflight Hematology (an inhouse study, FY 72: $15,000). The specific objectives of this effort are:
  - To develop and test procedures for collection of blood samples (micro and eventually macro) under spaceflight conditions
  - To perfect techniques for preparation of the samples inflight and preservation for retrospective biochemical analyses
  - To advance existing methods of single cell analysis for chemical and structural information. These techniques include electron microscopy, electron probe X-ray spectrometry and microspectrophotometry

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- To expand data analysis capability with emphasis on computerized pattern recognition and distribution profiles of cellular chemical constitutents

- To apply this information for the medical evaluation of man referable to his physiological performance at the cellular level during prolonged spaceflight.

During FY 72 this effort was directed toward the preliminary development of concepts and prototype hardware for tne acquisition, stabilization, and return of biological samples collected in flight.

4.1.H Blood Collection--National Science Foundation

No identified ongoing NSF supported activities are related directly to this area.

4.1.I Blood Collection--Social and Rehabilitation Service

No identified ongoing SRS supported activities relate directly to this area.

4.1.J Blood Collection--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area.

4.1.K Blood Collection--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

4.1.L Blood Collection--Veterans Administration

No identified ongoing VA conducted activities relate directly to this area.

4.2 BLOOD FRACTIONATION AND PRESERVATION

4.2.A Blood Fractionation and Preservation--Department of Agriculture

No identified ongoing USDA supported research is directly related to this area.

4.2.B Blood Fractionation and Preservation--Atomic Energy Commission

The AEC funds and administers contract supported studies in this area (FY 72: four onsite contracts, $522,000; one off-site contract, $15,000).

- In the Molecular Anatomy (MAN) Program at the Oak Ridge National Laboratory, work is in progress on the development of improved continuous-flow centrifugation for the separation of human leukocytes in quantities adequate for clinical use (transfusion). Current efforts are concerned with the modification of the rotor of the Aminco-IBM-NCI Blood Separator (Celltrifuge). Work on an axial flow rotor, a radial flow rotor, and two types of elutriators is in progress.

- Research on the storage of platelets in the frozen state is currently in progress at Brown University. The study investigates effects on platelet viability of different methods of freezing and thawing, including effects of agents that may protect the platelet throughout the complete freeze-storage-thaw cycle. Encouraging results are now being obtained with a plasma-DMSO (5 percent) medium.

- Ongoing studies at Oak Ridge National Laboratory (Biology Division) are concerned with the achievement of a better understanding of factors that contribute to the successful storage of erythrocytes (and other mammalian cells) in the frozen state. Particular interest now centers on the effect of different intracellular concentrations of glycerol on the hemolysis of freeze-thawed red cells and factors responsible for freeze injury in hamster cells.

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- Investigators at the Franklin McLean Memorial Research Institute (University of Chicago) have recently succeeded in isolating microgram quantities of erythropoietin from blood plasma of sheep rendered anemic by treatment with phenylhydrazine. In collaboration with scientists at the Oak Ridge National Laboratory (Biology Division) the Chicago investigators are now working to isolate quantities of pure sheep erythropoietin sufficient for clinical trials in patients with chronic kidney diseases. The clinical trials should establish whether or not the ovine hormone can be safely used in humans and if it is effective in the treatment of anemias associated with chronic impairment of renal function.

- At the Brookhaven National Laboratory, human marrow cells are being cultured in small diffusion chambers implanted in the peritoneal cavities of animals. Under these experimental conditions, no exchange of cells occurs between the culture and the animal host. Cell cultures implanted in mice have been found to undergo proliferation. Implantation in larger animals is now under study. This research, which is yielding information on factors that influence or control marrow cell replication and differentiation, may lead to improvements in blood cell transfusion (increased supply of specific cell types).

As discussed in Section 1.1.B (Atherosclerosis), AEC supported investigators are studying plasma lipoproteins from diverse points of view. Other research is concerned with the isolation and characterization of bovine factor XI (See Section 3.2.B, Arterial Thromboembolism).

4.2.C Fractionation and Preservation--Department of Defense

The Department of the Army funds and administers projects directed primarily at the fractionation and preservation

of blood and blood products (FY 72: 15 projects, total funding of $1,000,000).

The chief objectives of these studies include:

- Better preservation of stored blood and components in either liquid or frozen state until transfusion
- Examination of metabolic relationships of the red blood cell and membrane in terms of function and the effects on storage
- Quantification and characterization of essential components involved in the energetics of the red cell during prolonged storage
- Modification of blood storage conditions, such as pH variation of the chemical composition of anti-coagulants; interrelationships of various metabolic pathways in the cellular components to identify critical areas involved in aging of the cell, and evaluation of methods to reduce adverse effects of storage
- Measurement of storage-induced changes in the biochemical and physiochemical properties and stabilities of red cell membrane
- Determination of the properties, reactivity, and control mechanisms of a membrane proteinase, and the effect of platelets on red cell storage properties
- Utilization of various dyes to provide identification of significant changes in the composition and possible viability of the red cell
- Definition of metabolic reactions of the erythrocyte responsible for maintenance of viability
- Pharmacology and metabolism of adenine inhalation to hypoxia

- Measurement of megathrombocyte lifespan (radioautographically) of young platelets recently released from bone marrow to determine critical factors controlling platelet senescence

- Platelet respiration reserve capacity as an assessment of mitochondrial latent ability which can be revealed by graded decrements of osmolarity

- Investigations of the effect of plasma replacing preservative solutions on the stored red blood cell viability

- Identification of the origin of the debris in stored blood and investigation of methods to prevent or retard its formation

- Evaluation of the effect of methylene blue on hemoglobin function and determination of the optimum pH and concentration of phosphorus used to preserve red blood cell enzymes

- Manufacture and study of stroma-free hemoglobin solution

- The effects on blood composition and function of burns.

The Department of the Navy is sponsoring a program with frozen blood cells. This work has been carried on at the Navy Blood Research Laboratory in Boston. In FY 72 the aim was to determine the amount and function of granulocytes and platelets remaining in blood after the freezing, thawing, and washing procedures. It was determined that the red cells processed as frozen blood were virtually free of granulocytes and platelets, as measured by direct quantitation, or by residual antigenic activity. A number of preparation methods were compared, and the one which gave the greatest functional red cell yield with the minimum granulocyte and platelet carry-over was identified (funded at approximately $30,000).

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4.2.D Fractionation and Preservation--Environmental Protection Agency

No identified ongoing EPA supported efforts are related directly to this area.

4.2.E Fractionation and Preservation--Food and Drug Administration

The FDA's Bureau of Biologics funds and administers research on fractionation and preservation. This is being carried out under four separate projects. The effect on whole blood when stored at temperatures above 10°C is measured by changes in plasma hemoglobin. Under one project, several studies are being conducted on cryoprecipitated antihemophilic factor to determine the average AHF content of routinely produced material, the difference in yield from blood collected in ACD and CPD anticoagulants and the difference in yield when "cryo" is prepared from fresh plasma versus plasma kept below -18°C for six months.

A second project involves research comparing disc, moving boundary and cellulose acetate electrophoresis methods for control testing purposes; physical effects on serum albumin of repeated heating to reduce pyrogen content and an examination of the immunologic properties of serum albumin, aggregated albumin and albumin microspheres. Other research in this project includes studies of the maximum levels of isoagglutinins in immune globulin products; the effects of prior heating on stability of IgC during storage of human serum and the use of urokinase and ultracentrifugal measurements to predict stability of immune globulins during storage. Under the third and fourth projects, studies are

being carried out on the purification of factors IX and Xa; various properties of fibrinogen including heterogenity, cross-linkage, chain composition and nature of abnormal fibrinogens including Bethesda II and Oklahoma are being investigated, and finally research is being done on the effect of Echis Carinata venom on interaction of factors VIII, IX, and X.

In FY 72 this research was funded for approximately $50,000 from operating funds.

4.2.F Fractionation and Preservation--Health Services and Mental Health Administration

In FY 1972, the RMPS funded one project ($53,400) related to the preparation and use of frozen red cells. (No further information was available at the time this report was prepared.)

4.2.G Fractionation and Preservation--National Aeronautics and Space Administration

The Biomedical Research Division, NASA, funds and administers one inhouse study entitled "Special Inflight Hematology" related to this area (for topic description see Section 4.1.G).

4.2.H Fractionation and Preservation--National Science Foundation

No identified ongoing NSF supported activities are related directly to this area.

4.2.I Fractionation and Preservation--Social and Rehabilitation Service

No identified ongoing SRS supported activities relate directly to this area.

4.2.J Fractionation and Preservation--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area.

4.2.K Fractionation and Preservation--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

4.2.L Fractionation and Preservation--Veterans Administration

The VA funds, conducts and/or administers numerous studies related to fractionation and preservation. The following paragraphs describe those studies for which information was available. (No information on FY 72 funding was available for this report.) The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics.

- Deterioration of Young and Old Red Cells Stored at 4°C. Studies on young and old red cells separated by centrifugation have to date demonstrated that there is a difference in the degree of preservation of these cells during storage at 4°C. Estimates of metabolic adequacy as

measured by methylene blue uptake and ATP levels have indicated that young red cells deteriorate more rapidly than old cells when stored in the same or separate containers. These findings are in accord with the view that *in vivo* and *in vitro* (storage) aging are two distinct and independent series of events. They also indicate that storage deterioration is an intracellular phenomenon whose effects are not easily transmitted through the plasma.

- Studies of Enzymes that Convert Type B Blood to Type O. VA studies have been designed to selectively remove "exposed" galactose molecules from the cells, "uncovering" the type O glycoprotein coating these red blood cells and transforming the type B to type O cells.

Such uncovering has been accomplished with enzymes obtained from pathogenic bacteria known as *Clostridia* and pathogenic protozoa called *Trichomonas foetus*. However, these are scarce species and dangerous to work with. A comparable enzyme recovered from a simple nonpathogenic organism should have important uses in a broad range of investigations on the chemical structure of cell surfaces. Moreover, a potentially important application would be to produce universal donor type O red blood cells from types A or B.

An extractable bacterial enzyme that will convert B to C cells without otherwise producing damage was found in an extract of feces.

Bacteria have been grown from stool outside the body in a special culture broth, the enzyme then extracted from the broth. A culture of a mixture of unidentified fecal bacteria produced good quantities of extractable enzyme when incubated in the absence of air. The purity of the enzyme was improved and its potency was increased five to ten times above that of a preparation extracted directly from feces. It has converted type B red cells to type O without apparent damage.

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From the mixed culture of organisms a single specific species of bacterium has recently been isolated which can be propagated in pure culture, and which consistently produces the desired enzyme. The organism is classed as an anaerobic streptococcus. This successful isolation should make it possible to produce the enzyme in large volumes of culture medium free from contamination with unwanted enzymes released by other bacteria. This should provide large quantities of the enzyme suitable for processing to a highly purified state.

4.3 LABORATORY PROCEDURES AND CONTROLS

4.3.A Laboratory Procedures and Controls--Department of Agriculture

No identified ongoing USDA supported research is directly related to this area.

4.3.B Laboratory Procedures and Controls--Atomic Energy Commission

The AEC funds and administers contract supported studies in this area (FY 72: one onsite contract [fetal antigen study], totalling $250,000):

- Extensive research on the hepatitis antigen is currently in progress in the Molecular Anatomy (MAN) Program at the Oak Ridge National Laboratory. The hepatitis type B antigen is being characterized physically and chemically. Antisera against the virus and its constituent polypeptides are being prepared. Immune electron microscopy (a combination of electron microscopy and serological techniques) is proving useful in the study of viral structure and heterogeneity. A sensitive radioimmunoassay for the virus has been developed. This study is supported by the National Institute of Allergy and Infectious Diseases (NIAID).

- Investigators in the MAN Program are also conducting a comprehensive study of fetal antigens under joint NCI-AEC support. Research includes studies of immunization with fetal antigens (in rodents), search for fetal antigens in rodent tumors (immunofluorescence technique), and comparative testing (biochemical, physical, and biological tests) of fetal and tumor antigens.

Non-AEC support of onsite investigators in FY 72:

- NIAID (Hepatitis antigen study, MAN Program), $326,000
- NCI (Fetal antigen study, MAN Program), $650,000.

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4.3.C Laboratory Procedures and Controls--Department of Defense

In Fiscal Year 72 the Department of the Army conducted one study entitled "Formation of Debris in Stored Blood--Physiologic Significance and Removal by Filtration" (supported at $49,000).

The purpose of this study is to evaluate the role of filtration of stored blood in prevention of post-traumatic pulmonary insufficiency and to identify the origin of debris in stored blood and investigate methods to prevent or retard its formation.

4.3.D Laboratory Procedures and Controls--Environmental Protection Agency

No identified ongoing EPA supported efforts are related directly to this area.

4.3.E Laboratory Procedures and Controls--Food and Drug Administration

The FDA's Bureau of Biologics is using both in-house research and research contracts in conducting studies in the laboratory processing of blood. In-house studies are being performed comparing the accuracy and precision of the quantitative automated, antiglobulin titer and multiple dilution radioassay methods for measuring activity of Rho(d) Immune Globulin. Other in-house studies are being performed on the use of frozen reagent blood cells, the nature of particulate matter in blood typing serums and the stability of blood grouping and typing serums. Studies on research contracts are being conducted to investigate the application of large volume zonal

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centrifugation, purification, analysis and testing of biological materials including the concentration of HAAg for use in animal studies.

The Bureau of Biologics is conducting a multifaceted research program in the area of viral hepatitis oriented towards regulation of the following types of products: (a) *in vitro* diagnostics for donor testing, (b) safety of blood and blood products, (c) hyperimmune globulin and (d) vaccines. Definitive epidemiologic studies of post-transfusion hepatitis are being conducted by the New Jersey State Health Department under contract with the Bureau. Additional contracted support provides laboratory animals, primarily chimpanzees, for basic studies of viral hepatitis, type B and eventually for evaluation of product safety and potency in an animal model system.

The Bureau of Biologics expended $105,000 from its operating funds for research in this area in FY 72. An additional $320,000 was spent on research contracts in this area in FY 72.

4.3.F Laboratory Procedures and Controls--Health Services and Mental Health Administration

No identified ongoing HSMHA supported activities are related directly to this area.

4.3.G Laboratory Procedures and Controls--National Aeronautics and Space Administration

The Biomedical Research Division, NASA, funds and administers one in-house study entitled "Special Inflight Hematology" (for topic description, see Section 4.1.G).

4.3.H Laboratory Procedures and Controls--National Science Foundation

No identified ongoing NSF supported activities are related directly to this area.

4.3.I Laboratory Procedures and Controls--Social and Rehabilitation Service

No identified ongoing SRS supported activities relate directly to this area.

4.3.J Laboratory Procedures and Controls--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area.

4.3.K Laboratory Procedures and Controls--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

4.3.L Laboratory Procedures and Controls--Veterans Administration

No identified ongoing VA supported activities relate directly to this area.

4.4 UTILIZATION

4.4.A Utilization--Department of Agriculture

No identified ongoing USDA supported research is directly related to this area.

4.4.B Utilization--Atomic Energy Commission

No ongoing AEC work is directly concerned with this problem area.

4.4.C Utilization--Department of Defense

In FY 72, the Department of the Army funded and administered four projects ($364,000) directed primarily at problems associated with the utilization of blood and blood components.

The objectives of these projects included:

- Examination of the immunological aspects of blood banking for possible problems in blood transfusion therapy
- Investigation of the effects of blood loss on protein metabolism and the role of hormones under this stress
- Investigation of the effects of transfused material as treatment as well as possible adverse side effects on the recipient
- Determination of the clinical significance of shifts in the oxyhemoglobin dissociation curve and its effect on oxygen delivery to the patient's tissues.

The Department of the Navy is conducting a project on the survival time of HL-A matched platelets. The objective was to determine whether platelets from HL-A matched donors would survive longer in patients than would platelets from mismatched (random) donors. A panel of 100 volunteer platelet donors were assembled, and the HL-A types determined. An attempt was made to locate an HL-A identical donor for each patient. The project was abandoned when it became obvious that an impossibly large pool of donors would be necessary before HL-A identical donors could be located on a regular basis. (FY 72 funding: approximately $6,000.)

4.4.D Utilization--Environmental Protection Agency

No identified ongoing EPA supported efforts are related directly to this area.

4.4.E Utilization--Food and Drug Administration

The only research supported by the FDA's Bureau of Biologics in this category is a research contract with the University of Pittsburgh. The studies consist of a cytogenetic follow-up of intrauterine and exchange-transfused children. Approximately $24,000 was expended on this contract in FY 72.

4.4.F Utilization--Health Services and Mental Health Administration

In FY 72, the RMPS funded and administered one project ($50,466) related to the transfusion of frozen red cells. (No further information was available at the time this report was prepared.)

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4.4.G Utilization--National Aeronautics and Space Administration

No identified ongoing NASA supported activities are related directly to this area.

4.4.H Utilization--National Science Foundation

No identified ongoing NSF supported activities are related directly to this area.

4.4.I Utilization--Social and Rehabilitation Service

No identified ongoing SRS supported activities relate directly to this area.

4.4.J Utilization--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area.

4.4.K Utilization--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

4.4.L Utilization--Veterans Administration

The VA conducts and administers studies related to utilization. The following paragraphs describe the study for which information was available. (No information on FY 72 funding was available for this report.) The

projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics.

- Effects of Hemodilution (blood dilution) by Plasma-like Substances During and After Surgery. Studies in patients have clearly shown that blood viscosity rises after surgery. Hemodilution prevents much of the adverse circulatory effects of increased blood viscosity. Animal studies performed during FY 72 have shown that "physiological" hemodilution occurs after blood loss (i.e., blood is diluted by body fluids), lowering blood viscosity and improving circulation. However, the circulation doesn't return to normal until about 24 hours after the operation.

  In order to provide "therapeutic" hemodilution soon after bleeding, this VA study has used dilute solutions of dextran to replace blood volume. The effects of Dextran-70 vs. Dextran-40 have been studied. A new monitoring system, which uses temperature changes to measure the adequacy of the circulation (thermodilution) is being used to measure cardiac output almost constantly and the dosage of blood volume replacement solution can be carefully regulated. Such studies will be performed in patients undergoing surgical procedures during FY 73.

4.5 SYSTEMS MANAGEMENT

4.5.A Systems Management--Department of Agriculture

No identified ongoing USDA supported research is directly related to this area.

4.5.B Systems Management--Atomic Energy Commission

No identified ongoing AEC supported efforts are related directly to this area.

4.5.C Systems Management--Department of Defense

In FY 72, the Department of the Army supported one in-house project ($119,000) directed primarily at improvements in the management of blood and blood products.

The purpose of this study was to evaluate effectiveness of blood and/or blood products transfusion in combat treatment, with blood loss. Comparison testing of new techniques, equipment and reagents was maintained to focus on possible practical improvements that would benefit blood banking practices. Sickle cell hemoglobin identification by an automated screening system has shown feasibility; and approach to practical testing is under way. Frozen red cell storage techniques are being compared in order to develop a more useful, universally acceptable system for other blood banks.

4.5.D Systems Management--Environmental Protection Agency

No identified ongoing EPA supported efforts are related directly to this area.

4.5.E Systems Management--Food and Drug Administration

No identified ongoing FDA supported efforts are directly related to this area.

4.5.F Systems Management--Health Services and Mental Health Administration

In FY 72, the RMPS funded and administered two projects ($13,175) directed at improved blood system management:

- A supply demand study
- A blood bank information network.

No detailed information describing these projects was available at the time this report was prepared.

4.5.G Systems Management--National Aeronautics and Space Administration

No identified ongoing NASA supported activities are related directly to this area.

4.5.H Systems Management--National Science Foundation

No identified ongoing NSF supported activities are related directly to this area.

4.5.I Systems Management--Social and Rehabilitation Service

No identified ongoing SRS supported activities relate directly to this area.

4.5.J Systems Management--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area.

4.5.K Systems Management--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

4.5.L Systems Management--Veterans Administration

No identified ongoing VA supported activities relate directly to this area.

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4.6 TRANSPLANTATION

4.6.A Transplantation--Department of Agriculture

No identified ongoing USDA supported research is directly related to this area.

4.6.B Transplantation--Atomic Energy Commission

The AEC funds and administers contract supported studies pertinent to this area (FY 72: three onsite contracts, $1,185,000; six offsite contracts, $169,000).

These investigations include:

- A broad program of research in immunology that includes basic studies on histocompatability antigens, cellular and humoral responses to allografts, immunosuppression, and induction of specific tolerances
- Studies of certain aspects of the genetic control of the immune response (under study at the Brookhaven National Laboratory)
- Studies of methods of controlling infections in the immunosuppressed patient (under study at the Oak Ridge Associated Universities)
- Studies of immunologic tolerance in the marmoset (This small primate is unique in that it produces offspring that are permanent blood chimeras.)
- Cryobiologic studies conducted at the Oak Ridge National Laboratory (Biology Division) are in part concerned with the problem of organ preservation.

Specifically:

- Investigators at the Oak Ridge Associated Universities (Medical Division) conduct studies

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on human bone marrow transplantation, immunosuppression by total body irradiation delivered at varying dose rates, and control of infections in immunosuppressed patients. In addition, the immune competence of radiation and natural chimeras in mice and marmosets, respectively, is being evaluated in relation to the human studies.

- Extensive research is conducted at the Oak Ridge National Laboratory (Biology Division) on immunological aspects of bone marrow transplantation in the mouse. A major part of this research is concerned with the study of the graft vs. host reaction in the mouse radiation chimera and the status of the immune systems in animals that survive secondary disease (graft vs. host reaction). The chimera that survives the secondary disease has been found to have a defective immune system in that it is unable to change from 19 s antibody production to 7 s antibody production. Effects of thymocytes on the status and survival of radiation chimeras is also under study.

- Organ transplantations in histocompatability-matched dogs are conducted at the Mary Imogene Bassett Hospital. Studies at the Scripps Clinic and Research Foundation are concerned with the facilitation of transplantation by serum factors. Different approaches to the induction of immunologic tolerance are being investigated at the Scripps Clinic and Research Foundation, University of North Carolina, University of Oklahoma, Medical College of Virginia, and Brookhaven National Laboratory. Immunological research at the Brookhaven National Laboratory includes the study of genetic factors that may control the humoral antibody response. As a result of many observations in different strains of mice immunized with tetanus toxoid, the primary antibody response has been found to vary with genetic background and to correlate with the incidence of leukemia in these mouse strains.

- Cryobiologic studies at the Oak Ridge National Laboratory (Biology Division) are directly related to the problem of organ preservation. Progress is being made in the preservation of the mouse embryo in the frozen state.

Non-AEC support for onsite investigators during FY 72:

- NIAID (support of marmoset colony at Oak Ridge Associated Universities), $99,400
- U. S. Army (study microflora of immunosuppressed patients at Oak Ridge Associated Universities), $77,600

4.6.C Transplantation--Department of Defense

The Department of the Navy funds and administers two projects related to transplantation:

- Bone marrow transplantation program. The objective of this work was to establish a clinical research program in bone marrow transplantation for patients with aplastic anemia. During FY 72 a number of preparatory phases were completed, including the establishment of a blood cell separator facility, a sterile reverse isolation ward, and a complete protocol for marrow transplantation. The first patients treated under this program were transplanted in FY 73 (FY 72 funding: approximately $50,000).
- Preparation of antilymphocyte serum for NIH. This project was a contract to produce a pool of safe, effective antilymphocyte serum for a clinical trial in renal transplants. The research work involved studies to determine the best source of antigen, route and schedule of antigen injection, method of fractionation of whole antiserum, and tests for toxicity, immunosuppressive activity and *in vitro* correlates of graft prolongation activity. The contract is still continuing this year and will terminate with the delivery of a safe, effective product in amounts sufficient to treat 50 patients (FY 72 funding: approximately $150,000).

4.6.D Transplantation--Environmental Protection Agency

No identified ongoing EPA supported efforts are related directly to this area.

4.6.E Transplantation--Food and Drug Administration

No identified ongoing FDA supported efforts are directly related to this area.

4.6.F Transplantation--Health Services and Mental Health Administration

The RMPS funds and administers programs (FY 72: 11 contracts, $522,607) in transplantation. Included are:

- Organ Procurement Kidneys
- Transplant Salvage Coordination
- Prevention of Kidney Rejection
- Procurement and Preservation
- Organ Donor Programs.

(No detailed project descriptions were available at the time this report was prepared.)

4.6.G Transplantation--National Aeronautics and Space Administration

No identified ongoing NASA supported activities are related directly to this area.

4.6.H Transplantation--National Science Foundation

No identified ongoing NSF supported activities are related directly to this area.

4.6.I Transplantation--Social and Rehabilitation Service

No identified ongoing SRS supported research and/or rehabilitation activities relate directly to this area. The SRS provides third party payments for provision of care (which may involve participation in clinical research).

4.6.J Transplantation--Social Security Administration

No identified ongoing SSA supported activities relate directly to this area. The SSA provides third party payments for provision of care (which may involve participation in clinical research).

4.6.K Transplantation--Department of Transportation

No identified ongoing DOT supported activities relate directly to this area.

4.6.L Transplantation--Veterans Administration

The VA conducts and administers numerous studies related to transplantation. The following paragraphs describe those studies for which information was available. (No information on FY 72 funding was available for this

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report.) The projects are supported as part of the intramural research and patient care activities in VA hospitals and clinics.

- Studies in Experimental Transplantation Biology. This is a program of experimental transplantation biology as it applies to the transplantation of blood forming elements and other tissue organs in randomly bred animals. The activities of these studies have included or presently include:

  - The development of tissue typing techniques for blood cells which are necessary for selection of optimal donor-recipient pairs for transplantation

  - An attempt to define--in cooperation with other laboratories--the transplantation system in the dog as a model for experimental tissue exchange (At the present time reagents are being developed which clearly define white blood cell types in this species for transplantation purposes.)

  - A program has been initiated to develop heterologous and homologous antisera which are effective in suppressing the natural response of the host for rejection of an organ graft. (This antisera has been tested in a number of dogs and has proven to be useful in suppressing the skin graft rejection.)

  - Experiments have been performed to develop transfusion techniques for white cells which may aid in sustaining life during periods of poor blood formation (since many drugs and situations in which grafts are carried out involve patients who have suppressed blood formation and are, therefore, highly susceptible to infection). These experiments have progressed in the dog and may have considerable potential usefulness in man.

- The Kinetics of Lymphocytes. The kinetics of the lymphocytes, the blood cells most important to the body's immune system, have been determined in health

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and in chronic leukemia. Normally, the blood lymphocytes are in equilibrium with a cell pool of equal size distributed between the spleen and the bone marrow. The cells recycle between the blood and the tissues a dozen times each day, as an immunological patrol seeking foreign antigens. The normal small lymphocytes have a half-life of 18 days. In lymphocytic leukemia, the abnormal cells have a half-life of only four to five days, and the recirculating pool of cells is enormously enlarged. This indicates that, contrary to recent views, this form of leukemia results from accelerated production of an abnormal strain of shortlived lymphocytes.

The observations in normal humans improve our understanding of tissue immunity, which is involved in the rejection of transplanted organs, malignant growths, and certain infectious organisms. The findings in leukemia suggest new approaches for the control of the proliferative process.

- Pulmonary Function Following Autotransplanted Lungs. Extensive efforts have been expended in the study of pulmonary function of the reimplanted lung in the dog. The survival rate of lung reimplantation has risen from 42 percent to 63 percent through experience in the technique of resuture in the atrium, the pulmonary artery and the bronchus. Pulmonary function studies carried out by the split function technique of bronchospirometry illustrates that the reimplanted lung recovers approximately 85 percent of its original oxygen uptake and ventilation when measured in the presence of a normal right lung and in the absence of anatomic or surgical defect. Studies of the blood flow to the reimplanted lung, measured by flow probes and Fick principle indicates that normal response does not occur until 8 weeks following reimplantation despite the fact that oxygen uptake is considered as essentially normal. This work supports the hypothesis that clinical lung reimplantation is feasible, if pulmonary function can be maintained during the critical operative period.

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APPENDIX

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APPENDIX

This appendix is in two parts:

- Activities Index by Agency (Part A.1)
- Summary Program Support Data (Part A.2)

A.1 ACTIVITIES INDEX BY AGENCY

Listed in the following paragraphs, on an agency by agency basis, are the problem areas (with section numbers for reference) related to which each agency is currently conducting or supporting research activities.

- Department of Agriculture

  - Atherosclerosis (Section 1.1.A)
  - Hypertension (Section 1.4.A)
  - Environmental Respiratory Diseases (Section 2.2.A)
  - Emphysema and Chronic Bronchitis (Section 2.3.A)
  - Infectious Respiratory Diseases (Section 2.7.A)
  - Sarcoid and Granulomatous Lung Diseases (Section 2.8.A)
  - Pulmonary Vascular Disease (Section 2.10.A)
  - Hemophilia and other Bleeding Disorders (Section 3.1.A)
  - Disorders of Hemostasis Due to Platelet Abnormalities (Section 3.3.A)

- Atomic Energy Commission

  - Atherosclerosis (Section 1.1.B)
  - Coronary Heart Disease (Section 1.2.B)
  - Peripheral Vascular Disease (Section 1.3.B)
  - Hypertension (Section 1.4.B)
  - Stroke (Section 1.5.B)
  - Rheumatic and Other Valvular Heart Diseases (Section 1.7.B)
  - Cardiomyopathy (Section 1.8.B)
  - Arrhythmia (Section 1.9.B)
  - Cardiac Failure (Section 1.10.B)
  - The Normal Lung (Section 2.1.B)
  - Environmental Respiratory Disease (Section 2.2.B)
  - Emphysema and Chronic Bronchitis (Section 2.3.B)
  - Pediatric Obstructive Airway Diseases (Section 2.4.B)
  - Infectious Respiratory Diseases (Section 2.7.B)

- Pulmonary Vascular Disease (Section 2.10.B)
- Hyaline Membrane Disease of the Newborn (Section 2.11.B)
- Acute and Chronic Respiratory Failure (Section 2.13.B)
- Extrapulmonary Manifestations of Respiratory Diseases (Section 2.14.B)
- Hemophilia and Other Bleeding Disorders (Section 3.1.B)
- Arterial Thromboembolism (Section 3.2.B)
- Disorders of Hemostasis Due to Platelet Abnormalities (Section 3.3.B)
- Venous Thrombosis and Pulmonary Embolism (Section 3.4.B)
- Thromboembolism in Relation to Prosthetic Devices (Section 3.5.B)
- Microcirculatory Thrombosis (Section 3.6.B)
- Hemoglobinopathies (Section 3.7.B)
- Blood Collection (Section 4.1.B)
- Fractionation and Preservation (Section 4.2.B)
- Laboratory Procedures and Controls (Section 4.3.B)
- Transplantation (Section 4.6.B)
-

• Department of Defense

- Coronary Heart Disease (Section 1.2.C)
- Peripheral Vascular Disease (Section 1.3.C)
- Arrhythmia (Section 1.9.C)
- Shock (Section 1.11.C)
- The Normal Lung (Section 2.1.C)
- Infectious Respiratory Diseases (Section 2.7.C)
- Pulmonary Vascular Disease (Section 2.10.C)
- Hyaline Membrane Disease of the Newborn (Section 2.11.C)
- Hemophilia and Other Bleeding Disorders (Section 3.1.C)
- Hemoglobinopathies (Section 3.7.C)
- Fractionation and Preservation (Section 4.2.C)
- Laboratory Procedures and Controls (Section 4.3.C)
- Utilization (Section 4.4.C)
- Systems Management (Section 4.5.C)
- Transplantation (Section 4.6.C)

- Environmental Protection Agency

  - Coronary Heart Disease (Section 1.2.D)
  - Congenital Heart Disease (Section 1.6.D)
  - Rheumatic and Other Valvular Heart Diseases (Section 1.7.D)
  - Cardiomyopathy (Section 1.8.D)
  - The Normal Lung (Section 2.1.D)
  - Environmental Respiratory Diseases (Section 2.2.D)
  - Emphysema and Chronic Bronchitis (Section 2.3.D)
  - Allergic Airway Diseases--Asthma (Section 2.5.D)
  - Infectious Respiratory Diseases (Section 2.7.D)
  - Hemoglobinopathies (Section 3.7.D)

- Food and Drug Administration

  - Fractionation and Preservation (Section 4.2.E)
  - Laboratory Procedures and Controls (Section 4.3.E)
  - Utilization (Section 4.4.E)

- Health Services and Mental Health Administration

  - Atherosclerosis (Section 1.1.F)
  - Coronary Heart Disease (Section 1.2.F)
  - Hypertension (Section 1.4.F)
  - Stroke (Section 1.5.F)
  - Congenital Heart Disease (Section 1.6.F)
  - Rheumatic and Other Valvular Heart Diseases (Section 1.7.F)
  - Cardiomyopathy (Section 1.8.F)
  - Arrhythmia (Section 1.9.F)
  - Cardiac Failure (Section 1.10.F)
  - Environmental Respiratory Diseases (Section 2.2.F)
  - Emphysema and Chronic Bronchitis (Section 2.3.F)
  - Pediatric Obstructive Airway Diseases (Section 2.4.F)
  - Allergic Airway Diseases--Asthma (Section 2.5.F)
  - Infectious Respiratory Diseases (Section 2.7.F)
  - Hypersensitivity Lung Diseases (Section 2.9.F)
  - Hyaline Membrane Disease of the Newborn (Section 2.11.F)
  - Cystic Fibrosis (Section 2.12.F)

- Acute and Chronic Respiratory Failure (Section 2.13.F)
- Venous Thrombosis and Pulmonary Embolism (Section 3.4.F)
- Hemoglobinopathies (Section 3.7.F)
- Fractionation and Preservation (Section 4.2.F)
- Utilization (Section 4.4.F)
- Systems Management (Section 4.5.F)
- Transplantation (Section 4.6.F)

• National Aeronautics and Space Administration

- Coronary Heart Disease (Section 1.2.G)
- Peripheral Vascular Disease (Section 1.3.G)
- Hypertension (Section 1.4.G)
- Stroke (Section 1.5.G)
- Congenital Heart Disease (Section 1.6.G)
- Rheumatic and Other Valvular Heart Diseases (Section 1.7.G)
- Cardiomyopathy (Section 1.8.G)
- Arrhythmia (Section 1.9.G)
- Cardiac Failure (Section 1.10.G)
- The Normal Lung (Section 2.1.G)
- Environmental Respiratory Disease (Section 2.2.G)
- Emphysema and Chronic Bronchitis (Section 2.3.G)
- Acute and Chronic Respiratory Failure (Section 2.13.G)
- Extrapulmonary Manifestations of Respiratory Diseases (Section 2.14.G)
- Hemoglobinopathies (Section 3.7.G)
- Blood Collection (Section 4.1.G)
- Fractionation and Preservation (Section 4.2.G)
- Laboratory Procedures and Controls (Section 4.3.G)

• National Science Foundation

- Atherosclerosis (Section 1.1.H)
- Coronary Heart Disease (Section 1.2.H)
- Peripheral Vascular Disease (Section 1.3.H)
- Hypertension (Section 1.4.H)
- Stroke (Section 1.5.H)

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- Congenital Heart Disease (Section 1.6.H)
- Rheumatic and Other Valvular Heart Diseases (Section 1.7.H)
- Cardiomyopathy (Section 1.8.H)
- Arrhythmia (Section 1.9.H)
- Cardiac Failure (Section 1.10.H)
- The Normal Lung (Section 2.1.H)
- Hemophilia and other Bleeding Disorders (3.1.H)
- Arterial Thromboembolism (Section 3.2.H)
- Venous Thrombosis and Pulmonary Embolism (Section 3.4.H)
- Microcirculatory Thrombosis (Section 3.6.H)
- Hemoglobinopathies (Section 3.7.H)

• Social and Rehabilitation Service

- Coronary Heart Disease (Section 1.2.I)
- Stroke (Section 1.5.I)
- Congenital Heart Disease (Section 1.6.I)
- Rheumatic and Other Valvular Heart Diseases (Section 1.7.I)

• Department of Transportation

- Coronary Heart Disease (Section 1.2.K)

• Veterans Administration

- Atherosclerosis (Section 1.1.L)
- Coronary Heart Disease (Section 1.2.L)
- Peripheral Vascular Disease (Section 1.3.L)
- Hypertension (Section 1.4.L)
- Stroke (Section 1.5.L)
- Congenital Heart Disease (Section 1.6.L)
- Rheumatic and Other Valvular Heart Diseases (Section 1.7.L)
- Cardiomyopathy (Section 1.8.L)
- Arrhythmia (Section 1.9.L)
- Cardiac Failure (Section 1.10.L)
- Shock (Section 1.11.L)

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- The Normal Lung (Section 2.1.L)
- Environmental Respiratory Diseases (Section 2.2.L)
- Emphysema and Chronic Bronchitis (Section 2.3.L)
- Infectious Respiratory Diseases (Section 2.7.L)
- Pulmonary Vascular Disease (Section 2.10.L)
- Acute and Chronic Respiratory Failure (Section 2.13.L)
- Disorders of Hemostasis Due to Platelet Abnormalities (Section 3.3.L)
- Venous Thrombosis and Pulmonary Embolism (Section 3.4.L)
- Hemoglobinopathies (Section 3.7.L)
- Fractionation and Preservation (Section 4.2.L)
- Utilization (Section 4.4.L)
- Transplantation (Section 4.6.L)

A.2 SUMMARY PROGRAM SUPPORT DATA

Table 1 depicts the fiscal year 1972 (FY 72) funding level for identified related programs supported by 12 Federal agencies.

As depicted in Table 1:

- More than $81,000,000 in activities related to heart, blood vessel, lung and blood diseases and blood resources were supported
  - Heart and Blood Vessel Diseases related activities were funded at more than $53,000,000
  - Lung Diseases related activities in excess of $20,000,000
  - Blood Diseases related activities at more than $2,000,000
  - Blood Resources (including Transplantation) related activities in excess of $5,000,000
- The Health Services and Mental Health Administration supported more than 50 percent of the identified activities ($44,177,000)
- Funding data were not available for all identified activities (indicated by an asterisk in Table 1)
- No funding data were available for the sizable related program supported by the Veterans Administration. VA programs are supported as a part of intramural research and patient care activities in its hospitals and clinics.

Table 1

RELATED PROGRAMS FUNDING - FY 72

(in Thousands of Dollars)

PROBLEM AREA	United States Department of Agriculture	Atomic Energy Commission	Department of Defense	Environmental Protection Agency	Food and Drug Administration	Health Services and Mental Health Administration	National Aeronautics and Space Administration	National Science Foundation	Social and Rehabilitation Service	Social Security Administration	Department of Transportation	Veterans Administration	TOTAL
Atherosclerosis	1,040	500				180		104				••	1,824
Coronary Heart		4,443	611	3,121		13,668	840	(R)45	*2,332		724	••	25,784
Peripheral Vascular		*460	*				(R)28	R				(R)••	488
Hypertension	*	(R)540				1,128	171	94				••	1,933
Stroke		R				3,349	R	23	125			R	3,497
Congenital Heart				R		1,013	R	R	R			(R)••	1,013
Rheumatic Heart		R		R		698	R	20	R			R	718
Cardiomyopathy		(R)111		R		96	R	R				(R)••	207
Arrhythmia		1,000	*65			16,452	R	R				(R)••	17,517
Cardiac Failure		(R)				(R)	(R)18	R				(R)••	18
Shock			476									••	476
SUBTOTAL	1,040	7,054	1,152	3,121		36,584	1,057	286	2,457		724		53,475
Normal Lung		695	223	1,134			420	(R)212				(R)••	2,684
Environmental Respiratory	*	4,448		5,390		3,285	R					R	13,123
Emphysema and Bronchitis	*	R		R		1,627	R					(R)••	1,627
Pediatric Respiratory		R				1,850							1,850
Asthma				R		(R)94							94
Interstitial Respiratory													
Infectious Respiratory	*	150	713	R		43						••	906
Sarcoid and Granulomatous	*												
Hypersensitivity						R							
Pulmonary Vascular	*	R	155									R	155
Hyaline Membrane		30	12			R							42
Cystic Fibrosis						R							
Respiratory Failure		R				R	R					R	
Extra-pulmonary Manifestations		R					48						48
SUBTOTAL		5,323	1,103	6,524		6,899	468	212					20,529
Hemophilia	*	R	12					R					12
Arterial Thromboembolism		296						R					296
Hemostasis Disorders	*	R										••	
Venous Thrombosis		R				55		R				••	55
Prosthetic Devices		R											
Microcirculatory Thrombosis		R						R					
Hemoglobinopathies		1,064	77	147		(1,900)[1]	40	503				••	1,831
SUBTOTAL		1,360	89	147		55	40	503					2,194
Blood Collection		(R)*					15						15
Fractionation		(R)537	1,030		50	53	R					••	1,670
Laboratory Procedures		250	49		425		R						724
Utilization			370		24	50						••	444
Systems Management			119			13							132
Transplantation		1,354	200			523						••	2,077
SUBTOTAL		2,141	1,768		499	639	15						5,062
TOTAL	1,040	15,878	4,112	9,792	499	44,177	1,580	1,001	2,457		724		81,260

* = Projects were supported for which funding data is not available

•• = Projects supported as part of intramural research and patient care activities in VA hospitals and clinics - funding data not available

R = Related projects of agency are discussed in a cross-referenced section

(1900)[1] = These are NHLI funds which were expended by HSMHA under a reimbursement agreement. They are included in NHLI program totals (Part I, Volume V)

U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service
National Institutes of Health
National Heart and Lung Institute
DHEW Publication No. (NIH) 73–524

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BOOKBINDING
MIDDLETOWN, PA